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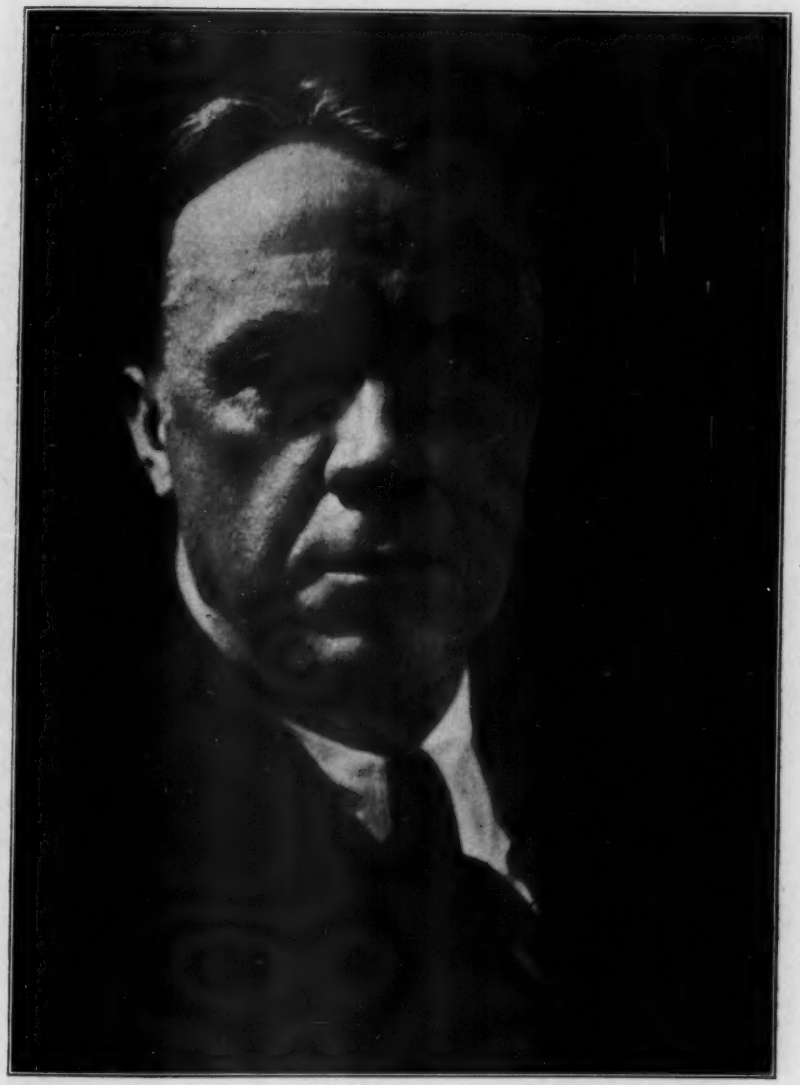

GEORGE MILLER MacKEE

Dedication

This issue is dedicated to Dr. George Miller MacKee, who on June 30, 1947, retired as Director of the Department of Dermatology and Syphilology of the New York Skin and Cancer Unit and the New York Post-Graduate Medical School and Hospital. Doctor MacKee has given liberally of his time, effort and wisdom to American dermatologic periodicals. From 1909 to 1918, he was editor of the *Journal of Cutaneous Diseases, Including Syphilis* and from 1918 to the present time has been a member of the Editorial Board of the ARCHIVES.

The contributors to this volume are former associates, assistants and students of Dr. MacKee, and it is unfortunate that more space is not available in this issue so that other colleagues could also have demonstrated their respect and loyalty by contributing to it. The pleasant task of collecting the material was done by his successor, Dr. Marion B. Sulzberger.

We thank Dr. MacKee for his wholehearted and generous cooperation during the many years he has served as one of the members of the editorial board.

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TRIBUTE TO DR. GEORGE MILLER MacKEE

From His Pupils, Associates and Friends of the New York Skin and Cancer Unit

MARION B. SULZBERGER, M.D.
NEW YORK

ONLY a very small number of the over one thousand pupils and associates of George MacKee have been able to show their appreciation and affection by a contribution to this honor volume of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY. I appreciate the opportunity to express, as best I can, the esteem and gratitude of the hundreds of friends and disciples who through the years have profited by MacKee's teaching and example.

No one who worked with or under MacKee has failed to become a better dermatologist, a better physician or a better human being because of his contacts with the Chief. Despite the fact that some have held him to be "a hard man to know," his great qualities as teacher and leader have touched and transmuted each and every one of us.

It is not easy to select from among MacKee's many great qualities those which should be mentioned in this short tribute, but I think that the following selection includes those qualities which all of us would agree are characteristic:

MacKee has always been fair, unprejudiced and impartial. No consideration of origin, of race, of belief, of sex or of social or economic position has ever influenced him one whit in his attitude toward or treatment of his co-workers. All who were willing to give honest service have ever been welcome to the Chief and to his department. The constitution of the present staff of the Department of Dermatology and Syphilology of the New York Skin and Cancer Unit and the Post-Graduate Medical School of the New York University–Bellevue Medical Center attests to MacKee's true democratic spirit—in practice as well as theory.

MacKee has ever been modest and faithful. On no occasion has he been willing to take sole credit for his accomplishments. He has always insisted that his fellow workers were those who deserved the major honors. Time after time, at our annual staff dinners and elsewhere, MacKee has told us of his group of staunch friends, of Dave Satenstein, of Fred Wise and Isadore (Ike) Rosen, Bill Abramowitz, Maxie Scheer, Katherine Sullivan and Stella Perkins, and many others, and his voice has inevitably become choked with emotion as he described what he felt

he owed to these co-workers and companions. Each and every man and woman of MacKee's staff and student body knew that beyond any doubt the Chief could be counted on and that he would back them to the limit, whatever their scrapes or troubles.

MacKee has never failed in wisdom or equanimity. In all my nineteen years of association with him, I have on every occasion gained something of value from his advice—whether on medical matters, on personal affairs or on other and wider problems. Trying as we younger folk often must have been, selfish and inconsiderate in adding some petty personal burden to the Chief's heavy load, none of us has ever found MacKee angry, impatient or inconsiderate. He seemed to be able to draw on a limitless store of patience and understanding. To come into his presence in his small unpretentious office, with its walls covered with the pictures of the dermatologic great, was always like coming out of the din and clangor of turbulent battle into a quiet and shaded place, full of comfort and strength.

This is a woefully incomplete account of how we, his pupils and associates, feel about George MacKee, but I hope that it may serve to show in some measure why MacKee has been so successful in building and organizing a great teaching and research institute in American dermatology.

By nature's endowments and through the school of rigid self discipline, MacKee is a chief in every true sense of the word—a man to be relied on, to be followed and to be loved by those who know him.

GEORGE MILLER MacKEE, M.D., AN OUTSTANDING DERMATOLOGIST AND LOYAL FRIEND

HOWARD FOX, M.D.
NEW YORK

I FELT highly flattered on being asked to write the story of Dr. MacKee's accomplishments to honor him in this issue of the ARCHIVES. I first met George MacKee in Fordyce's Clinic at the New York University in 1906, shortly after the appearance of his article on staining of the Spirochaeta pallida.[1] I wanted some information on the subject, and McKee gave it willingly. This was the beginning of an unbroken close friendship for over forty years. Although he was a young man beginning to learn dermatology, as I was, I was greatly impressed by the serious interest in his work and prophesied that he would eventually become a great leader in our specialty. He made the same impression on Dr. George T. Jackson and others, including my father. Needless to say, my prophesy came true.

Dr. MacKee is a perfect example of a self-made man, as he said "self educated and to a large extent self trained." He was born in 1878 in Jersey City, N. J., of American parents of Scotch, Irish, Dutch and French ancestry, and moved to Stamford, Conn., at the age of 2. His early training consisted of a grammar school education, one winter in a business school and three years as a medical student in the New York University (then called New York University and Bellevue Hospital Medical College). In his school years, he worked as a bicycle and printer's mechanic, from the age of 13 to 17. He became a splendid athlete and helped himself through medical school by giving athletic instruction, playing professional basket ball and acting as a deep sea fisherman and beach guard at Ocean Grove, N. J., during the summer vacations. For several years after graduation, it was necessary for him to engage in professional athletics and to practice general roentgenologic work and physical therapy. He joined Dr. Fordyce's Clinic at the New York University in 1903.

George MacKee was the type who would have made his mark as either a professional or business man. The secret of his great success was his ambition and extraordinary capacity for work. He was a serious, kindly man who treated his assistants well. He had their whole-

1. MacKee, G. M.: The Spirochæta Pallida in Syphilis, with Special Reference to Goldhorn's Rapid Staining Method, New York M. J. **83**:588, 1906.

hearted support, which was shown when he resigned from the College of Physicians and Surgeons and was offered the professorship of the Department of Dermatology at the New York Post-Graduate Medical School and Hospital. Approximately twenty-eight of his assistants resigned with him and helped later to build up the largest dermatologic clinic in the world.

The first piece of great fortune which befell MacKee was when Dr. Fordyce made him his chief of clinic at Columbia, after he had left the New York University. As Fred Wise said in his delightful sketch, MacKee "never stood in need of incentive or stimulus from anybody, but it was Fordyce who inspired him and encouraged him."[2] One of the greatest kindnesses shown by his chief to MacKee was making him editor of the *Journal of Cutaneous Diseases, Including Syphilis.* He held this position from 1909 to 1918. While it proved a difficult job, it was a liberal education for MacKee, who took the work as seriously as anything in his career. It was a great help to him in writing excellent English and in learning dermatologic terminology.

Dr. MacKee dedicated the first volume of his book on roentgen rays to Dr. Fordyce and after his death wrote a beautiful tribute to him in the ARCHIVES.[3] Dr. MacKee's editorial experience made him a valuable member of the editorial board of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY since 1918, the *Journal for Investigative Dermatology* since 1939 and *Dermatology and Venereology* since 1946.

OUTSTANDING ACCOMPLISHMENTS

The Historian's files of the American Dermatological Association contain so much material about George MacKee that I thought it best to ask him what he considered his most important accomplishments. He described, in modest terms, two items that had given him the greatest satisfaction; one was his book on roentgen rays, and the other was the formation of a self-contained dermatologic department. He added the statement, with which I cannot agree, that these were "the only two of any importance."

Dr. MacKee's greatest achievement was undoubtedly the publication of his book on "X-Rays and Radium in the Treatment of Diseases of the Skin."[4] The basic knowledge needed to write this invaluable book, now in its fourth edition, was his early experience in practice. As he said, he practiced deep and superficial roentgen therapy, radium

2. Wise, F.: Dr. George Miller MacKee, J. Invest. Dermat. **8**:277 (June) 1947.

3. MacKee, G. M.: John Addison Fordyce, Obituary, Arch. Dermat. & Syph. **12**:268 (Aug.) 1925.

4. MacKee, G. M.: X-Rays and Radium in the Treatment of Diseases of the Skin, Philadelphia, Lea & Febiger, 1921.

therapy and physical therapy while endeavoring to become a dermatologist. Probably his comprehensive knowledge of all these subjects is unique among dermatologists. In his writing on the "Arithmetical Computation of Roentgen Dosage,"[5] he had the valuable assistance of Dr. John Remer, who was an excellent mathematician.

Dr. MacKee wrote me that he believed that his "x-ray book, especially the first two editions, was of practical value to dermatology." This was modesty personified for a book that revolutionized the treatment of skin diseases with roentgen rays. It was published at a time when therapeutic resourcefulness in our specialty was considerably less than at present. The technic is eminently safe, as has been found by the successful treatment of thousands of cases of ringworm of the scalp. MacKee also suggested that his early work in physical therapy kept cutaneous physical therapy in dermatology instead of in physical medicine.

In 1915, I had to attend a meeting of the American Medical Association in San Francisco and persuaded George to go with me. The trip was an eye opener for him as he had never previously traveled any distance. We went by way of the Canadian Rockies and spent a week in the Glacier National Park on the way home. While crossing the Bad Lands of South Dakota, George became disgusted with the trip. However, as we approached Banff, he came to life with a vengeance and soon became enamored of the beautiful mountain scenery. On this trip we did some traveling by horseback, which gave George a chance to exhibit his great talent as a photographer. The trip pleased him so much that for a number of years he spent his vacations in the Canadian Rockies, where he became a splendid mountain climber. He was later made a member of the Canadian and of the American Alpine clubs.

One of the few occasions on which I have seen George become greatly excited occurred at 7 a. m. in our hotel room in Glacier Park. He woke me up with a shout, which made me think that at least a grizzly bear was about to enter our room. I rushed to the window and was delighted to see a beautiful reflection of the mountains in the lake, which we both photographed, and we admitted that it was difficult to tell which were the mountains in the distance and which was the reflection.

Because of overwork in writing the first edition of his book on roentgen rays and spending his vacations in strenuous mountain climbing, MacKee unfortunately contracted pulmonary tuberculosis, which kept him out of work for five years. Fortunately, his prac-

5. MacKee, G. M.: Arithmetical Computation of Roentgen Dosage, J. Cutan. Dis. **37**:783 (Dec.) 1919.

tice was kept up by Dr. Earl D. Crutchfield (deceased), Dr. Lawrence K. McCafferty (deceased), Dr. M. J. Gibans, Dr. Blanche Norton, Dr. Clarence H. Peachey, Dr. Chris Halloran and especially Dr. George C. Andrews, who was in charge for several years. Invaluable help was given by his faithful and efficient secretary, Miss Katherine M. Sullivan. As I had originally recommended Miss Sullivan to MacKee, I did not feel too guilty about introducing him to mountain climbing in the Canadian Rockies.

The second important achievement in MacKee's opinion was the formation of a self-contained dermatologic department, beginning in Fordyce's Clinic and continuing when the Skin and Cancer Hospital was combined with the New York Post-Graduate Medical School and Hospital. This made it possible to obtain satisfactory full time graduate training in dermatology without going to Europe, and almost without going out of the department. It is hardly necessary to say that when the two institutions were united, the dermatologic clinic became the largest in the world, with a staff of one hundred and seventeen dermatologists, and, of course, one of the most famous. MacKee made the following important comment: "Such self-contained departments throughout the United States, with basic medical science research, have helped to prevent dermatology from being absorbed by medical departments." MacKee also told me that approximately seven hundred physicians had obtained their training in dermatology in his organization. For the success of his department, MacKee insists on giving full credit to his large, loyal and capable staff, especially to his well known key men, Fred Wise, Isadore Rosen, Elias W. Abramowitz, David L. Satenstein and Max Scheer, and, during the last fifteen years, to his efficient departmental secretary, Miss Stella Perkins.

Dr. MacKee has had some academic title in a medical school during most of his professional life, having served in the New York University, Columbia University and the New York Post-Graduate Medical School. Probably the greatest academic honor he received was his recent appointment as professor emeritus of clinical dermatology by Columbia University. This honor came after the separation of Columbia University and the Post-Graduate Medical School. It is also the first occasion for a member of an affiliated institution to receive an emeritus degree from Columbia.

In Fordyce's Clinic at the New York University, Dr. MacKee was instructor in dermatology and syphilology, and in the same clinic at the College of Physicians and Surgeons, he served successively as instructor (1910-1918), assistant professor (1918-1926) and professor of dermatology and syphilology (1926-1933).

At the New York Post-Graduate Medical School, MacKee became professor of clinical dermatology and syphilology and executive officer

of the department, including the Skin and Cancer Hospital, the name of which was changed to the Skin and Cancer Unit of the New York Post Graduate Medical School and Hospital. Other academic appointments included lecturer on dermatology and syphilology at the Trudeau School of Tuberculosis (1927-1933), lecturer at the Angle School of Orthodontia (1906-1912) and lecturer on dermatology and syphilology in the Fone's School for Dental Prophylactic Technicians (1913-1917).

SOCIETY MEMBERSHIPS

In local societies Dr. MacKee is an active member and past president of the New York Dermatological Society, an honorary member and past president of the Manhattan Dermatological Society, honorary member of the Brooklyn Dermatological Society, president (1941) of the Association of Dermato-syphilologists of Greater New York, past chairman of the Section of Dermatology and Syphilology of the New York Academy of Medicine (1917), charter member and past president of the New York Roentgen Society and past president of the Alumni Federation of the New York University.

The most important national society to which MacKee belongs is the American Dermatological Association, of which he was president in 1926 and treasurer from 1930 to 1947. He became a member in 1911 and recently resigned to become a senior inactive member. In the American Medical Association, he was a charter member of the Council on Physical Therapy, resigning in 1940. He was also chairman of the Section on Dermatology and Syphilology in 1932. He was chairman of the Section on Dermatology and Syphilology of the Medical Society of the State of New York in 1934. He was president of the American Academy of Dermatology and Syphilology in 1941 and a charter member of the American Board of Dermatology and Syphilology, resigning in 1938. He was president of the Society for Investigative Dermatology in 1937. He is an active member of the American Roentgen Ray Society, the American Radium Society and a fellow of the American College of Radiology. He has been an honorary member of the Stamford (Conn.) Medical Society since 1946, and was formerly a member of the American Urological Association (1904-1910).

Dr. MacKee has received abundant recognition from foreign countries for his scientific publications. He is a corresponding member of the Argentine, British and Hungarian Dermatological Societies and an honorary member of the Cuban, French and Japanese Dermatological Associations, the London Dermatological Society, St. John's Hospital Dermatological Society of London, the Wiener Dermatologische Gesellschaft, the Radiological Society of North America and the Venezuelan Society of Dermatology and Venereology (1948).

HOSPITAL APPOINTMENTS

Dr. MacKee's appointments were made in the following hospitals: St. Vincent's, as roentgenologist (1905-1910) and consulting dermatologist (1910 to date); Presbyterian, as assistant attending dermatologist (1910-1926); New York Post-Graduate (1926-1947); Reconstruction Unit, as attending dermatologist and syphilologist (1926-1947); Welfare, First Division, as attending dermatologist (1939-1944). He is now consulting dermatologist to Passaic General Hospital (since 1905), Stamford Hospital (since 1905), Port Chester Hospital (since 1905), Yonkers Hospital (since 1906), St. Lukes Hospital (since 1932), Holy Name Hospital, Teaneck, N. J. (since 1939) and St. Joseph's Hospital, Stamford, Conn. (since 1946). He was formerly consulting dermatologist to Sea View Hospital (1915-1934).

TRIBUTE

Two recent events meant a good deal to MacKee. One was a surprise dinner given in 1939 to celebrate his forty years in medicine. He was presented with a bound volume, of which there is only one copy, containing photographs and tributes from each of his thirty-three office assistants. Dr. William H. Guy was largely responsible for this honor paid to his former chief. The other event, at which I had the pleasure to be present, was the annual staff dinner on March 16, 1946. It was a farewell tribute to Drs. MacKee, Wise and Rosen, on which occasion each was presented with a handsome gold watch by the staff. Both Wise and Rosen were retiring according to custom at the age of 65. MacKee was urged to continue but was willing to serve only one more year.

It is obvious from this brief sketch that George MacKee has fulfilled my prophesy of becoming a great leader in dermatology. He has held almost every possible dermatologic honor and merits his retirement from active practice, which he recently announced. He realizes that a large number of honorary positions chiefly add to his reputation. He also knows, as I do, the definition of a hospital consultant, namely, one who is rarely called in for consultation.

We have traveled together twice to California, once to Mexico and many shorter distances. We have served together for years in various dermatologic societies. While disagreeing on a few minor questions, we have remained close friends for over forty years. His advice to me about roentgen rays in my early years was invaluable. My advice to him was not to work too hard.

I have long admired George for his courage, honesty, kindness and fairness to his associates, his administrative ability and his extraordinary capacity for work. He is a perfect example of a most successful self-made man and a loyal friend. I have never known another

man who could work as hard and accomplish as much as George MacKee has since his illness. As he is five years younger than I am, I expect that he will outlive me. In his delightful home on the outskirts of Stamford, Conn., I wish him all possible good fortune in the coming years.

140 East Fifty-Fourth Street (22).

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TREATMENT OF BASAL CELL EPITHELIOMA BY INJECTION OF TISSUE EXTRACTS

A Further Report

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IN A PREVIOUS report[1] the results of treatment of basal cell epitheliomas with tissue extracts prepared from human spleen and liver were described. The small number of normal human organs available for this work limited the number of patients who could be accepted for treatment. Obviously, the immediate problem resolved itself into the location of more plentiful sources of the effective principle.

In the laboratory constant emphasis has been placed on the problem of determining the nature of the principle. It is hoped that a more thorough understanding of its nature will be helpful in eventually pointing the way toward synthesis, as has been the case with some of the vitamins. Our more immediate approach, however, has been of the "cut and try" type, a testing of extracts of organs which were readily available.

Fardon, Brotzge and Loeffler,[2] for example, in working with heterologous tissue extracts, demonstrated that rabbit spleen pulp is effective in increasing resistance to transplantable mouse carcinoma 15091a, and, likewise, a deproteinized beef spleen extract showed some power to induce resistance to the same mouse carcinoma. However, they concluded that these extracts "failed to induce a resistant state . . . comparable to that elicited by the homologous tissue pulps and extracts."

This research was made possible partly through a grant from the Lillia Babbitt Hyde Foundation.

From the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University, and the Institutum Divi Thomae, Cincinnati.

1. Amersbach, J. C.; Walter, E. M., and Sperti, G. S.: Treatment of Basal Cell Epithelioma by Injection of Tissue Extracts: A Preliminary Report, Arch. Dermat. & Syph. **54**:119-132 (Aug.) 1946.

2. Fardon, J. C.; Brotzge, G. C., and Loeffler, M. K.: The Role of Homologous and Heterologous Tissue Extracts in the Establishment of the Resistant State Against Carcinoma, Stud. Inst. Divi Thomae **3**:69-80, 1941.

Lewisohn [3] had also found a beef spleen extract to cause regression of mouse sarcoma 180.

From these results it seemed likely that extracts of heterologous tissues, such as those of beef spleen and lamb liver, might prove effective in the treatment of human cancer, even though they might be less effective than homologous tissue extracts.

THE PREPARATION OF SPLEEN AND LIVER EXTRACTS

Beef spleens and lamb livers were obtained from freshly slaughtered animals. The extracts were prepared by the same procedure used for the extracts of human tissues.

The liver and the spleen extracts were prepared separately. The tissues were weighed, trimmed of all fat and extraneous connective tissue, ground thoroughly and then added to a volume of distilled water corresponding to the weight of the tissue, i. e., 100 cc. of water per hundred grams of spleen. The suspension was frozen and thawed three times, one day being allowed for each freezing and thawing procedure. The proteins were then precipitated by adding increasing concentrations of 95 per cent alcohol to the *brei*. First, alcohol was added to a final concentration of 50 per cent, and the mixture was allowed to stand for two hours. Finally, the concentration was raised to 80 per cent, and the mixture was allowed to stand for one day and then filtered free of tissue and precipitated protein. The extract was concentrated *in vacuo* approximately to the volume of distilled water added originally. This water solution was then extracted with three separate portions of ether of a total volume equal to that of the water solution. The ether solution was discarded, and the water solution was evaporated almost to dryness. The residue was made up to the desired concentration with distilled water.

A concentration of tissue extract equivalent to 15 Gm. of tissue was used. The p_H of the extract was adjusted to 6.5 to 7 with potassium hydroxide, and the extract was boiled for thirty minutes. After standing in the refrigerator overnight the solution was filtered. The extract was then put in serum bottles and was boiled for thirty minutes on each of three successive days. Each sample of extract prepared was tested for toxicity by injecting into a guinea pig the same amount to be used subsequently on a patient. Ill effects were not shown either by the animals or by the patients.

CLINICAL PROCEDURE

The clinical procedure was the same as that employed with the human extracts reported in the previous paper.[1] Patients with small

3. Lewisohn, R.: Effect of Subcutaneous Injections of Concentrated Spleen Extract on Mouse Sarcoma 180, Surg., Gynec. & Obst. **66**:563-576, 1938.

basal cell epitheliomas varying from pea size to 3 or 4 cm. across in the longest dimension were selected indiscriminately as they appeared in the clinic service. Before any treatment was given, a colored photograph

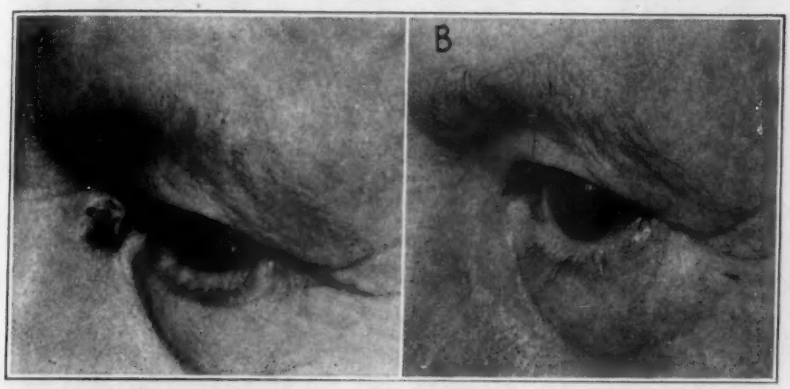

Fig. 1 (case 31).—*A*, basal cell epithelioma on the left inner canthus before treatment; *B*, after twenty-three injections of beef spleen.

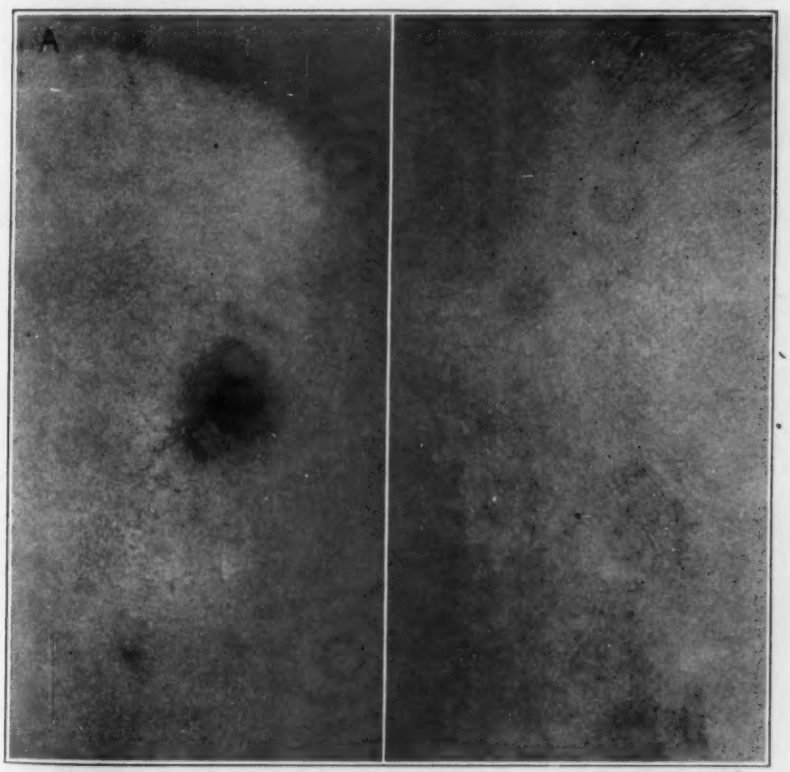

Fig. 2 (case 37).—*A*, intraepidermic basal cell epithelioma on the scalp before treatment; *B*, after nine injections of beef spleen.

*Case Histories of Patients Treated with Tissue Extracts**

Case	Patient	Sex	Age	Location and Description of Lesion	Pathologic Report	Treatment	Duration of Treatment	Result
22	I. N.	M	45	Pea-sized lesion with raised borders on tip of nose	Infiltrating basal cell epithelioma	Human spleen; 7 injections	3/15/44 to 7/19/44	Complete regression
23	V. S.	F	70	Large pea-sized nodular lesion on inner canthus of upper right eyelid	Basal cell epithelioma	Human spleen, 23 injections	5/24/44 to 10/23/45	Failed to regress
24	B. G.	M	33	Large pea-sized eroded area with pearly borders on right cheek	Basal cell epithelioma	Human spleen; 20 injections	5/31/44 to 4/4/45	Complete regression
25	G. B.	M	69	Dime-sized lesion with central ulceration and pearly borders under left lower eyelid (report of anaplastic during treatment)	Basal cell epithelioma	Human liver; 10 injections	6/12/44 to 1/22/45	Complete regression
26	B. W.	M	55	Nickel-sized lesion with rolled pearly borders on right preauricular area	Basal cell epithelioma	Human liver; 34 injections	6/14/44 to 4/23/45	Complete regression
27	J. K.	M	53	Large ulcerated lesion 2 by 3 cm. on left side of cheek	Recurrent basal cell epithelioma	Human liver; 11 injections	9/13/44 to 1/15/45	90% regression; patient failed to continue treatment
28	C. F.	F	39	Quarter-sized raised lesion with central ulceration and pearly borders on right cheek, recurrence of previous surgical excision	Basal cell epithelioma	Human liver; 38 injections beef spleen; 7 injections	10/4/44 to 4/3/46	Complete regression
29	H. S.	M	73	Large pea-sized lesion with central ulceration and pearly borders on right cheek	Basal cell epithelioma	Beef spleen; 26 injections	1/10/45 to 4/3/46	Complete regression
30	E. R.	M	62	Lesion 1.27 by 3.81 cm. with central ulceration and pearly borders on left preauricular area	Basal squamous cell epithelioma	Beef spleen; 16 injections	1/10/45 to 6/6/45	Regression slow; lesion excised
31	C. M.	M	67	Pea-sized lesion with central ulceration and pearly borders on left inner canthus	Basal cell epithelioma	Beef spleen; 22 injections	1/17/45 to 7/11/45	Complete regression
32	M. S.	F	36	Small pea-sized raised pearly lesion on right side of nose	Basal cell epithelioma	Beef spleen; 11 injections	1/17/45 to 5/16/45	Complete regression

33	D. L.	F	47	Dime-sized lesion previously treated with electric needle on right temple	Basal cell epithelioma	Beef spleen; 10 injections	2/21/45 to 8/22/45	Complete regression
34	A. F.	F	62	Dime-sized raised lesion on right cheek	Senile keratosis	Beef spleen; 10 injections	4/18/45 to 10/8/45	90% regression; patient failed to continue treatment
35	C. L.	M	51	Raised pea-sized pearly lesion on right side of nose	Basal cell epithelioma	Beef spleen; 10 injections	5/2/45 to 11/14/45	Complete regression
36	C. F.	F	40	Dime-sized raised pearly lesion with central ulceration on forehead	Infiltrating basal cell epithelioma	Beef spleen; 8 injections	6/18/45 to 11/19/45	Complete regression
37	C. C.	M	82	Quarter-sized raised black crusted lesion on scalp	Intraepidermic basal cell epithelioma	Beef spleen; 9 injections	6/18/45 to 10/29/45	Complete regression
38	C. R.	M	45	Large pea-sized pearly raised lesion under right eye	Basal cell epithelioma	Beef spleen; 8 injections	7/9/45 to 11/26/45	Complete regression
39	M. D.	M	70	Raised superficial lesion 1.27 cm. in diameter on right temple	Basal cell epithelioma	Lamb liver; 13 injections	7/30/45 to 5/6/46	90% regression; still under treatment
				Red lesion 1.27 cm. in diameter, 0.64 cm. raised with central ulceration on back of neck	Basal squamous cell epithelioma	Lamb liver; 15 injections	7/30/45 to 5/6/46	Complete regression
40	I. S.	F	69	Pea-sized ulcerated lesion on bridge of nose	Prickle cell epithelioma	Lamb liver; 6 injections	9/12/45 to 11/28/45	Complete regression
41	R. O.	M	39	Pea-sized ulcerated lesion with pearly borders on left nasolabial fold	Basal cell epithelioma	Lamb liver; 13 injections	10/23/45 to 5/29/46	70% regression; still under treatment
42	B. S.	F	62	Quarter-sized lesion with central ulceration and pearly borders on left temple	Basal cell epithelioma	Lamb liver; 18 injections	10/23/45 to 5/29/46	70% regression; still under treatment
43	J. B.	M	..	Dime-sized raised pearly lesion on center of forehead	Basal cell epithelioma	Beef spleen; 16 injections	11/14/45 to 4/17/46	70% regression; still under treatment
44	M. W.	M	48	Pea-sized lesion with central ulceration and pearly borders on lower eyelid near left inner canthus	Basal cell epithelioma	Lamb liver; 19 injections	11/7/45 to 5/1/46	90% regression; still under treatment
45	E. M.	F	80	Large raised nodular lesion 5.08 by 3.81 cm. and 1.27 cm. raised with central ulceration on right temple	Infiltrating anaplastic epithelioma	Beef spleen; 9 injections	4/1/46 to 6/3/46	Somewhat improved; still under treatment

* The preceding 21 case histories are tabulated in the preliminary reports.[1]

was taken of the lesion, and a biopsy was performed for pathologic diagnosis of the lesion. The patient was then given a series of weekly intradermal injections varying from 0.25 to 2.5 cc. of the extract. At each treatment the lesion was infiltrated, until the lesion and the surrounding tissue for about ¼ inch (0.64 cm.) became blanched and hard. After the lesion had regressed clinically a post-treatment biopsy was taken to determine whether any malignancy remained.

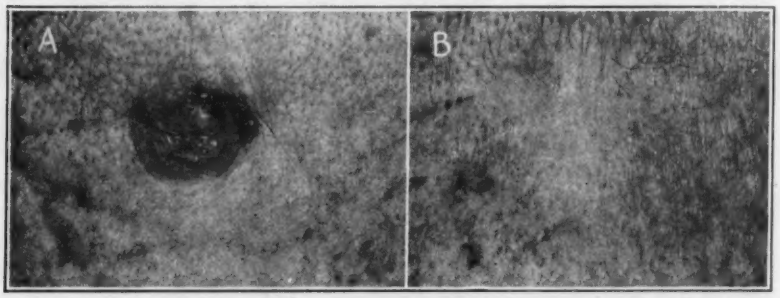

Fig. 3 (case 39).—*A*, spinobasal cell epithelioma on the back of the neck before treatment; *B*, after fourteen injections of lamb liver.

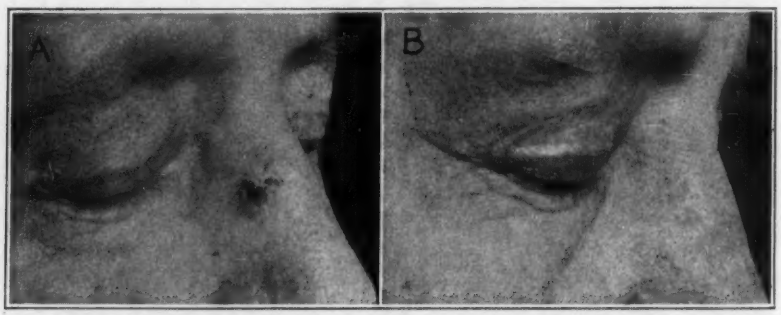

Fig. 4 (case 40).—*A*, prickle cell epithelioma on the bridge of the nose before treatment; *B*, after six injections of lamb liver.

RESULTS

Results are reported for 24 patients, of whom 3 were treated with human spleen extract, 3 with human liver extract, 12 with beef spleen extract, 5 with lamb liver extract, and 1 with both human liver and beef spleen extract. Actually, six lesions were treated with lamb liver extract, since 1 patient had two lesions. The case histories are given in the accompanying table, and photographs of several patients before and after treatment are shown.

It may be well to summarize the 45 cases reported in the previous and in the present paper. In the seventeen lesions treated with human spleen extract there were eleven complete regressions, two slow regres-

sions in which the lesion was excised, two which had regressed 50 per cent and 80 per cent respectively when last seen, and two failures. In the ten lesions treated with human liver extract, there were seven complete regressions, one slow regression in which the lesion was excised and two which had regressed 90 per cent when last seen. In the 12 cases in which treatment was with beef spleen extract, there were eight complete regressions, one slow regression in which the lesion was excised, one with 90 per cent regression when last seen and two still under treatment showing definite regression. In the case in which treatment was with both human liver extract and beef spleen extract, there has been complete regression. In the 5 cases with six lesions treated with lamb liver extract there were three complete regressions and three lesions still under treatment which showed 70 to 90 per cent regression.

It will be noted that the present series of lesions includes a spinobasal cell epithelioma and a prickle cell epithelioma. These more malignant epitheliomas likewise regressed completely when treated with the tissue extract.

SUMMARY

Of the forty-six lesions reported in this and in the preceding paper, two failed to respond, four were excised because of slow regression, five showed 50 to 90 per cent regression when last seen, five were still under treatment at the time of writing but had shown definite regression, and thirty showed complete regression.

NOTE.—In the previous publication [1] references to the work by Albert Braunstein on the use of spleen therapy in the treatment of experimental animals and in 2 cases of human external cancer were unintentionallly omitted:

Braunstein, A.: The Problem of the Prophylaxis of Cancer from the Immuno-Biological Standpoint, M. Woman's J. **51**:25-32, 1944; Ueber die Bedeutung der Milz in der Geschwulst—Immunität und Therapie (Ein neues Verfahren der Krebsbehandlung): I. Experimenteller Teil, Berl. klin. Wchnschr. **48**:2029-2031, 1911.

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CONTACT ROENTGEN THERAPY

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NEW YORK

IT WAS twelve years ago that I first saw the Chaoul contact therapy apparatus [1] used by Prof. Woodburn Morrison at the Cancer Hospital in London, and since then I have been interested in this subject. There are only a few Chaoul machines in the United States, which were imported from Germany prior to the war. Here the Philips contact therapy apparatus is more widely used. Therefore my paper will be mostly about the Philips machine. I will speak as a clinician of its merits and shortcomings.

At the risk of repetition I will briefly describe the construction of contact therapy tubes. In the Chaoul type of tube the short target-skin distance is made feasible by mounting a gold-plated nickel target at the extreme end of the tube, where it serves not only as a target but also as a filter, because the beam of roentgen rays passes through it. This filtration produces a rather strongly filtered beam. In the Philips tube, the filament is the grounded electrode near the end of the tube and the target is set back a short distance. The roentgen ray beam in the Philips tube does not pass through the target but only through a thin glass window and a cap of plastic material which has a filtration equivalent to 0.2 mm. of aluminum. When the face of the tube is in contact with the skin, the target-skin distance is 18 mm. This distance may be slightly increased by the use of cones, so that target-skin distances of the order of 2 and 4 cm. are in everyday use.

The physical factors of low voltage contact roentgen therapy have been described by Quimby,[2] Braestrup [3] and others. Maynard [4] observed that the ray quality of the Chaoul tube is equivalent to a half-value

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Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., June 4, 1946.

1. Chaoul, H.: Die Behandlung Bösartiger Geschwülste durch eine der Radiumtherapie angepasste Röntgenbestrahlung, München. med Wchnschr., **81**: 235-239, 1934.

2. Glasser, O.; Quimby, E. H.; Taylor, L. S., and Weatherwax, J. L.: Physical Foundations of Radiology, New York, Paul B. Hoeber, Inc., 1944.

3. Braestrup, C. B., and Blatz, I. H.: Physical Factors in Low Voltage "Contact" Roentgen Therapy, Radiology **35**:198-205, 1940.

4. Maynard, W. V.: Measurements of Low Voltage X-Rays, Brit. J. Radiol. **9**:215-238, 1936.

layer of 3.3 mm. of aluminum, and Quimby [5] wrote that this is considerably harder than the radiation obtained with standard superficial therapy apparatus in common use in this country, which produces radiation with a half-value layer of about 1 mm. of aluminum when operated at 100 kilovolts without a filter. She concluded that any advantage in the Chaoul equipment lies not in the quality of the radiation but in the shape of the tube, which permits its insertion into the body cavities, and in the short distances that can be used.

However, the shape of the tube is no longer a special advantage, because with modern shock-proof equipment and intracavitary visual cones one can treat lesions in the mouth and other body orifices even more readily and more accurately than is possible with contact therapy tubes. Therefore, the chief advantage of the Chaoul tube is its short target-skin distance, and the same statement may be applied to the Philips tube.

COMPARISON WITH RADIUM APPLICATORS

In regard to the quality of the radiation from the Philips tube, one must keep in mind that, although it is loosely compared to that produced by radium applicators, it is different. The radiation from the Philips tube, as already mentioned, is of a soft quality, and even when passed through a filter of 2.5 mm. of aluminum the half-value layer, according to Quimby, is only 1.6 mm. of aluminum. In the treatment of cutaneous diseases, radium plaques so softly filtered are not generally used but a filter of 0.5 mm. of platinum or 2 mm. of brass is applied. This cuts out all the beta rays and allows 100 per cent gamma radiation. This radiation has a half-value layer of about 1.2 cm. of lead.

CHART 1.—Braestrup has compared the depth doses of contact roentgen therapy with those obtainable with radium. He stated that a radium tube 20 mm. long with 0.5 mm. of platinum filtration applied at 7 mm. distance from the skin will give the same proportionate depth dose at 1 cm. below the surface as the Philips contact therapy tube operating at 44 kilovolts unfiltered. This seeming similarity is due largely, as Braestrup has explained, to the factors of distance rather than to any similarity in the quality of radiation.

CHART 2.—With Dr. Quimby's permission I am including a chart from her article which shows the curves of depth dosage with the Philips contact therapy tube and with a radium plaque at a distance of 2 cm. By placing the radium at a distance of 2 cm. instead of 1 cm. and by using a plaque instead of a tube the whole analogy is changed. From this chart one can readily see that there is no similarity between the quality of unfiltered radiation with a Philips tube and that of the

5. Quimby, E. H., and Focht, E. F.: Dosage Measurements in Contact Roentgen Therapy, Am. J. Roentgenol. **50**:653-668, 1943.

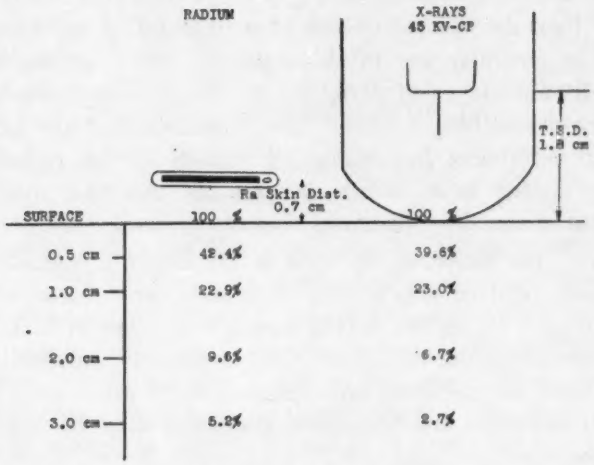

Fig. 1.—Comparison of depth doses of contact roentgen therapy with those obtainable with radium. (Courtesy of Dr. C. B. Braestrup.)

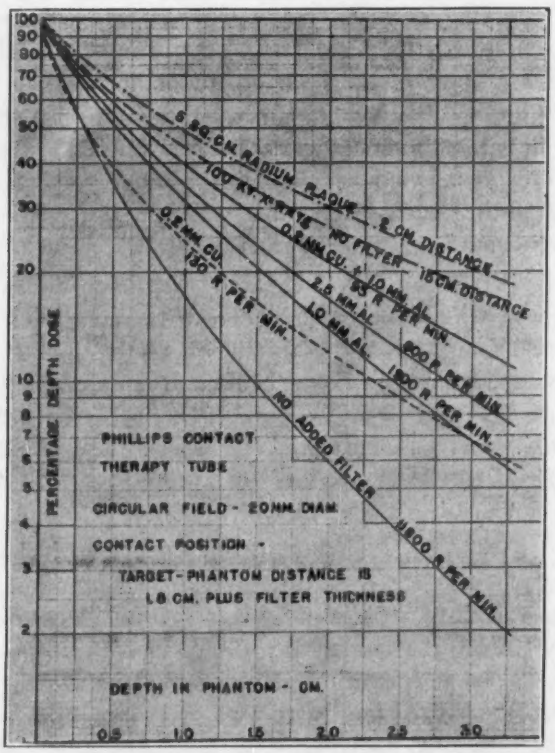

Fig. 2.—Curves showing percentage depth doses for unfiltered and filtered 44 kilovolt roentgen rays. (Courtesy of Dr. E. H. Quimby and Dr. E. F. Focht.)

radium applicator. Although the distribution of the radiation within the tissues under conditions mentioned by Dr. Braestrup may be similar, the quality of the radiation is entirely different. Whether quality of itself influences the biologic effects is a question, but certainly the clinical results are not the same with the Philips tube and the radium applicator.

In this connection Braestrup called attention to the differences in the rate of dosage. It would be practically impossible to duplicate the high rate of dosage with roentgen rays because it would require 35 Gm. of radium to do so. In other words, the Philips tube delivers 10,000 to 16,000 r per minute, whereas with ordinary radium applicators screened with 0.5 mm. of platinum twenty to forty hours are necessary to produce such a quantity of radiation. That the biologic effect is influenced by the rate of dosage is established in a general sense. This is well

TABLE 1.—*Comparison of Depth Doses of Roentgen Rays and Radium* *

	Roentgen Rays							Radium
Type	Grenz	Contact	Low Voltage		Intermediate	High Voltage		
Kilovolts	10	45	65	100	135	135	200	Gamma Rays
Filter (mm.)	0	0	2 aluminum	0	3 aluminum	0.25 copper +1 aluminum	0.50 copper +1 aluminum	0.5-1.0 pt.
Distance	10 cm.	1.8 cm.	15 cm.	15 cm.	15 cm.	15 cm.	50 cm.	1 cm.
Field diameter	2.5 cm.	2.5 cm.	2.5 cm.	2.5 cm.	2.5 cm.	2.5 cm.	2.5 cm.	...
0 (surface)	7700	208	111	134	114	109	105	201
0.5 cm.	100	100	100	100	100	100	100	100
1.0 cm.	...	48	86	79	89	91	93	60
3.0 cm.	...	5.6	37	32	53	58	67	15
5.0 cm.	...	1.2	17	12	28	37	47	7.0
10.0 cm.	...	..	..	2.2	..	9.2	19	..

* From Braestrup and Blatz (Radiology 35: 198-205, 1940).

illustrated by comparing the number of roentgens necessary to produce erythema if given in a single dose with the number necessary if the dose is divided and given over several days. The differences in the rates of dosage expressed here are doubtless sufficient to modify noticeably the clinical effect.

TABLE 1.—In Table 1, Braestrup has compared the depth doses of roentgen rays of various voltages that are commonly used and the gamma rays of radium from a tube at a distance of 1 cm. It will be seen that in order to obtain a uniform dose of 100 r at a depth of 0.5 cm. it is necessary to vary the surface dose within a wide range extending from 7,700 r for grenz rays to 105 r for high voltage radiation. Also one notes in this chart the influence of distance on depth dose for the radiation produced at 200 kilovolts at 50 cm. target-skin distance has a much larger depth dose than gamma radiation from a distance of 1 cm. This relationship would be completely altered if the radium were placed at a greater distance. Roentgen ray apparatus with a capacity

of 1,000,000 volts is required to produce the equivalent of gamma radiation.

TABLE 2.—The effect of filtration on the distribution of the dose is shown by Braestrup in table 2, using radiation produced by the Philips tube which runs at a constant potential of 45 kilovolts and at 2 milliamperes. As stated, the inherent filtration is equivalent to 0.2 mm. of aluminum. Without additional filter a surface dose of 13,000 r gives a dose at a depth of 1 cm. of 3,000 r. When a filter of 1 mm. of aluminum is added a surface dose of 8,250 r gives a dose at a depth of 1 cm. of 3,000 r. When the filtration is increased to 0.2 mm. of copper and 1 mm. of aluminum the same depth dose at 1 cm. can be obtained by giving a surface tissue dose of 6,450 r. In other words, the percentage of depth dose at 1 cm. is doubled from 23 per cent to 46 per cent by using a filter of 0.2 mm. of copper and 1 mm. of aluminum.

TABLE 2.—*Effect of Filtration on Dose Distribution* *

Voltage	45 kilovolts constant potential	M.A. 2.0	
Filter	0.2 mm. aluminum	1.2 mm. aluminum	0.2 mm. copper, 1 mm. aluminum
High voltage	0.28 mm. aluminum	1.04 mm. aluminum	3.8 mm. aluminum
Distance	1.8 cm.	2.1 cm.	2.1 cm.
Diameter of field	2.5 cm.	2.9 cm.	2.9 cm.
(r/min. in air)	9,500	1,470	245

	Tissue Dose (Roentgens)		Tissue Dose (Roentgens)		Tissue Dose (Roentgens)	
Surface	100%	13,000	100%	8,250	100%	6,450
1 cm.	23.0	3,000	36.3	3,000	46.6	3,000
2 cm.	6.7	870	14.4	1,190	24.3	1,560
3 cm.	2.7	350	6.7	553	14.1	905
5 cm.	0.6	78	1.9	157	5.5	354
Time	1'20"		5'18"		24'36"	

* From Braestrup and Blatz (Radiology **35**: 198-205, 1940).

TREATMENT OF EPITHELIOMAS

The results in the treatment of epitheliomas with the Philips tube are no better and often are not as good as those obtained with standard superficial therapy machines with unfiltered radiation produced at 60 or 100 kilovolts. The advantage of the Philips tube lies in the protection of deeper structures and the rapidity with which large doses can be given.

With the Philips apparatus I use 8,000 r to 16,000 r, unfiltered except for the filtration inherent in the tube. This is given in divided doses in eight to twelve exposures over a period of two to three weeks. The size of the dose is changed according to the thickness, or depth, and size of the epithelioma, the amount of subcutaneous tissue, the proximity of bone or cartilage and the patient's age and type of skin. These large doses cause severe reactions, which, however, are superficial and heal with surprisingly little scarring.

My impression is that I get just as good clinical results in the treatment of small superficial epitheliomas with 6,000 r. to 8,000 r in divided dosage at 60 to 100 kilovolts as I get with 10,000 r to 16,000 r in divided dosage with the Philips tube. However, many epitheliomas are larger than the area that the Philips tube covers. The end of the tube is circular and 2.5 cm. in diameter. This adequately covers an epithelioma 1 cm. in diameter. It is not adequate for larger epitheliomas unless multiple exposures are given or the target-skin distance is increased. For this reason, the small size of the Philips tube is often inadequate and the size of the field covered by standard superficial therapy units is an advantage.

The rate of dosage is, of course, a little different with each technic. With my Philips apparatus it requires 3.5 seconds to deliver 1,000 r, whereas with the superficial therapy unit of 100 kilovolts it requires two and a half minutes to deliver 1,000 r.

As stated, the small dose less than 1 cm. in depth of the radiation produced by the Philips tube makes it especially suitable for treatment of cancer of the eyelids. The ability to give large doses of this type of radiation within a few seconds is a great advantage in treating lesions on the lids because one cannot hold the lids still long. Also, the eyeball can be successfully shielded against contact roentgen therapy. These advantages give it great superiority over radium or roentgen rays produced by ordinary superficial therapy apparatus for the treatment of cancer of the eyelids.

TREATMENT OF HEMANGIOMA

By using the tables of Paterson and Parker,[6] the output in gamma roentgens of small radium applicators, which I have used repeatedly for the treatment of hemangiomas, may be calculated. One of these applicators is rectangular and measures 1.5 by 3 cm. and is composed of three silver tubes within a brass tray, which gives a total filtration equivalent to 2 mm. of brass. This applicator contains 90 mg. of radium and is used at a distance of 1 cm. on a balsam wood block. The period for the erythema dose is three and a half hours and for the therapeutic dose for hemangiomas two and a half hours. The output of this applicator, as computed from the charts of Paterson and Parker, is 675 gamma roentgens in two and a half hours at a distance of 1 cm. Another radium applicator I use is 2 by 4 cm. and contains 75 mg. in silver tubes in a brass box. It is applied at a distance of 1 cm. for three and a half hours for the treatment of angiomas. This dose is

6. Paterson, R., and Parker, H. M.: Dosage System for Gamma Ray Therapy, Brit. J. Radiol. **7**:592-632, 1934.

computed to be 655 roentgens. Such a treatment is applied at intervals of three months three to five times on thick or deep hemagiomas, or fewer times on more superficial ones. When I refer to thick or deep angiomas, I mean those between 5 and 10 mm. thick. For deeper ones I may use implants. For the more superficial, radium plaques properly screened and in contact with the skin are best.

In the treatment of hemangiomas one is interested especially in the cosmetic result. This is a completely different objective from that in the treatment of epithelioma, in which the cure rather than the appearance is paramount. To obtain a good cosmetic result the aim should be to avoid local cutaneous reactions. Hence the erythema dose which is obsolete in the treatment of cancer is important in the treatment of hemangiomas and some other cutaneous diseases. The aim is to cause the disappearance of the angioma while causing the least possible injury to the skin.

If the gamma rays of radium are used it takes about 1,000 r to produce a perceptible faint erythema, whereas with the relatively soft radiation produced by the Philips tube filtered through 2.5 mm. of aluminum a perceptible erythema is probably produced by about 300 r. One is able with the radium applicator to give doses of 675 r without producing an erythema, whereas only about one-half this amount with the Philips apparatus causes erythema. In other words, one can apply roughly three times as many gamma roentgens as roentgens from the Philips apparatus, if the erythema reaction of the skin is accepted as the limit.

The technic advised by Pendergrass [7] for the treatment of hemangiomas with the Philips apparatus has formed the basis of my work. Using radiation filtered through 2.5 mm. of aluminum he gives 200 to 250 r at intervals of six weeks for a total of four to six doses. This Philips technic gives a total dose of 1,000 to 1,500 r, which compares with a total dose of 2,250 to 3,750 gamma roentgens from the radium applicator. Each dose of 250 r from the Philips apparatus is equivalent to about three fourths of an erythema dose, whereas with the radium each dose of 675 r is roughly equivalent to two thirds of an erythema dose.

It appears from these figures that the quality of radiation from the Philips apparatus is not as suitable as that from radium applicators for the treatment of hemangiomas. Likewise it seems that the harder radiation from the Chaoul tube would be superior to the radiation from the Philips tube for this purpose. I believe that Dr. Pendergrass prefers and generally uses the Chaoul tube.

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7. Pendergrass, E. P., and Hodes, P. J.: Further Experiences with Chaoul Therapy, Radiology **37**:550-559, 1941.

These conclusions are in line with my clinical experience [8] and with that of many other radiologists and dermatologists. Pfahler [9] stressed the importance of the hard quality of radiation in the gamma rays of radium for the treatment of hemangiomas. As he stated, "Some good results have been obtained and reported by various authors with each kind of radiation—high voltage and high filtration, low voltage and moderate filtration and contact therapy with very low voltage and little filtration. . . ." Pfahler stated that it was his impression that for the treatment of hemangioma the highly filtered radium rays (gamma rays) give the most uniformly good cosmetic results. MacKee [10] also favored radium for the treatment of hemangiomas, but preferred less filtration.

TREATMENT OF WARTS

The Philips tube is specially useful in the treatment of warts, because of the large output. The average dose unfiltered for small warts is 2,500 to 3,500 r. This is delivered in a few seconds. Fortunately, the soft quality of the radiation and the short distance eliminate worries about deep injuries which may follow the use of higher voltages and longer target-skin distances. For plantar warts a dose of 3,500 r is often used advantageously.

TREATMENT OF KERATOSES

For the treatment of senile and seborrheic keratoses, the average dose is 1,200 r unfiltered. The skin about the keratosis is closely shielded. The cosmetic results from this treatment are good.

MECHANICAL CONSIDERATIONS

The chief advantage of the Philips tube, like the Chaoul tube, lies in the tremendous output made possible by the short target-skin distance. It saves a great deal of time. Also, the absorption of the major portion of the output within the upper centimeter of tissue gives relative protection to deeper structures.

Both Braestrup and Quimby have warned that considerable amounts of stray radiation develop around the Philips tube. The operator, to be safely protected, must wear a lead-rubber fluoroscopic apron and lead rubber gloves whenever near the tube during treatments if more than two or three are given daily.[11]

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8. Andrews, G. C.: Diseases of the Skin, ed. 3, Philadelphia, W. B. Saunders Company, 1946; Treatment of Angioma Based on Ten Years' Experience at the Vanderbilt Clinic, Arch. Dermat. & Syph. **37**:573-582 (April) 1938.

9. Pfahler, G. E.: The Treatment of Hemangioma, Radiology **46**:159-170, 1946.

10. MacKee, G. M.: X-Rays and Radium in the Treatment of Diseases of the Skin, ed. 3, Philadelphia, Lea & Febiger, 1938.

11. Stenstrom, W.; Quimby, E. H., and Pendergrass, E. P.: Report of Research and Standardization Committee, Am. J. Roentgenol. **43**:118-125, 1940.

The Philips apparatus is portable. This feature is of little practical value. If the portable feature were done away with and safety and stability were substituted for it by the use of a protective screen and a different tube stand, wider use of the apparatus would be encouraged.

The dental type of extension of the tube stand is cumbersome and unreliable, because it is so weak that the weight of the cable continually pulls the tube out of position. A good counterbalanced tube stand, such as the Chaoul or Solus machines have, would improve the Philips apparatus.

The smaller cones with the Philips machines are of little value. I have observed that accurate treatments can be made only if the patient lies down on a table and if the lesion is exposed through a hole cut in a piece of sheet lead, using a cone far larger than the size of the lesion. Then if the patient or the tube moves a fraction of an inch, the lesion remains in focus.

Aside from these shortcomings, the Philips tube and apparatus possess exceptional merits for the treatment of small superficial epitheliomas and hemangiomas and for the treatment of keratoses and warts. It has special advantages for the treatment of epitheliomas on the eyelids.

DISCUSSION

DR. ANTHONY C. CIPOLLARO, New York: We have been fortunate in hearing Dr. Andrews, who simplified a complicated subject. I would like to discuss contact therapy for a few minutes. What will it do for dermatology? Dr. Andrews has already pointed out its limitations. It has some uses, but the uses are limited to a few localized diseases like the epitheliomas and the hemangiomas.

We have here essentially an x-ray machine which delivers radiation of approximately 50 kilovolts. In that respect it is just like any ordinary x-ray machine if it is throttled down to 50 kilovolts, and so the effects to be expected from its use in contact therapy should be the same as those to be expected from an ordinary x-ray machine.

When Chaoul first advocated this method of therapy, he had three things in mind. First, he wanted to save time. He wanted to deliver a great many roentgens in a short period of time. Who wants to give 8,000 roentgens in one minute for a cutaneous disease, even a basal cell epithelioma? Certainly, one would not think of treating an epithelioma in the office with 8,000 roentgens all at one time. Second, it is difficult to measure time with exposures of such great intensity unless one has a special clock or automatic timer which measures in one twentieth of a second. The second reason that Dr. Chaoul advocated the use of this type of therapy is that he desired to limit the radiations to a well circumscribed volume of tissue. By so doing, destructive caustic doses of roentgen rays are applied to the diseased parts and the surrounding normal tissues escape damage. Third, Chaoul thought that the results with contact therapy were similar to those obtained with radium and superior to those obtained with conventional roentgen ray therapy. He ascribed this superiority to the fact that radium and

contact therapy were applied close to the skin. Most radiologists and dermatologists agree that a lesion responds equally well to either form of radiation provided that it is properly administered.

DR. GEORGE CLINTON ANDREWS, New York: One purpose I had in presenting this paper was the hope that the manufacturers of the Philips apparatus might improve this machine.

The principle of using a short target-skin distance, and thereby protecting the deeper structures, is an excellent one.

There is a great deal of stray radiation, which necessitates weaing a lead-rubber apron and lead-rubber gloves. Also, the tube holder is a flexible extension of the type used in dental apparatus, which leads to inaccuracy because the heavy weight of the cables pulls the tube out of position.

LUPUS ERYTHEMATOSUS TELANGIECTODES

PAUL E. BECHET, M.D.
ELIZABETH, N. J.

IN 1888 Radcliffe Crocker [1] first described a telangiectatic form of lupus erythematosus characterized by symmetric persistent circumscribed patches on both cheeks, which on palpation were decidedly thickened and shot through with dilated blood vessels. The extensor surface of the hands was the seat of patchy persistent erythema, resembling chilblain, which after involution showed atrophic scarring. According to Crocker the patches on the cheek simulated the red paint on a clown's face. Under the term "erysipelas perstans faciei," Kaposi,[2] in 1872, also called attention to the deep red patches on the face with purpura preceding the onset of lupus erythematosus acutus disseminatus.

For the past thirty-five years, with one exception no articles on the subject have appeared in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY, and there are not more than seven unchallenged case reports in that journal. It is not described in the textbooks with the exception of Ormsby's book,[3] in which it has been given a paragraph. There is a report of a fatal case of lupus erythematosus acutus disseminatus with disseminated telangiectasis by Robertson and Klauder,[4] who stated, "The association of disseminated telangiectasis with lupus erythematosus has not, to our knowledge, been reported in the literature." The patient had a patch of lupus erythematosus discoides on her scalp for three years before the appearance of purplish telangiectatic patches on her breasts, which gradually spread to the abdomen and legs. Shortly thereafter the face became the site of irregular ovoid scaly lesions of a rosy pink color and somewhat infiltrated. They were of the discoid type but later spread over the entire face and neck, becoming erythematous and of such a deep red color as to resemble the eruption in erysipelas. Death

Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., June 13, 1946.

1. Crocker, H. R.: Diseases of the Skin: Their Description, Pathology, Diagnosis and Treatment, Philadelphia, P. Blakiston Son & Co., 1888.

2. Kaposi, M.: Neue Beiträge zur Kenntniss des Lupus erythematosus, Arch. f. Dermat. u. Syph. **4**:36-78, 1872.

3. Ormsby, O. S.: A Practical Treatise on Diseases of the Skin, Ed. 5, Philadelphia, Lea & Febiger, 1937.

4. Robertson, W. E., and Klauder, J. V.: Lupus Erythematosus Acutus Disseminatus: Report of Fatal Case Associated with Disseminated Telangiectasis, Arch. Dermat. & Syph. **8**:487-497 (Oct.) 1923.

occurred three and one-half years after the appearance of the disease on the scalp, five months after the incidence of the discoid lesions on the face and six weeks after the appearance of constitutional symptoms.

At a meeting of the Chicago Dermatological Society, Harry R. Foerster [5] presented a case for diagnosis. The patient had had advanced pulmonary tuberculosis which was apparently quiescent. The cutaneous lesions first appeared on the feet and later on the hands and face. Their appearance varied in intensity, becoming worse in hot weather, and consisted of cyanotic streaks and blotches. Small horny plugs formed on the lateral and the plantar surfaces of the feet. The lesions were painful. The facial lesions consisted of pigmented inflammatory telangiectatic and scaly macules. The ears, face, trunk, palms and soles showed more or less pronounced telangiectasia. In the discussion Ormsby stated that the clinical picture was one of vascular disturbance of the skin due to tuberculosis, and whether it was called lupus erythematosus, lupus pernio or sarcoidosis did not matter. Finnerud also stated the belief that the condition was due to tuberculosis but considered the clinical picture as atypical lupus erythematosus. Foerster, in closing, stated that the condition was considered a telangiectatic form of lupus erythematosus with a toxemia of underlying tuberculosis as the causative factor. Ormsby [6] presented a case for diagnosis at the clinical session of the Dermatological Conference of the Mississippi Valley Dermatological Society in Chicago. The patient, a woman, was first seen nine years previously. At that time there was moderate erythema with scaling and telangiectasia on both cheeks and on the forehead. Subsequently, punctate atrophic lesions developed. For a year prior to presentation the patient had been given gold sodium thiosulfate with good results, the active process had disappeared, and only the atrophy and the telangiectasia were present. In the discussion Pusey and Michelson suggested the diagnosis of telangiectatic lupus erythematosus, which was accepted by Ormsby. Ormsby [7] later presented another case in a man aged 53. His cheeks were covered by a symmetric eruption consisting of pale red elevated plaques, at the margins of which were innumerable dilated blood vessels. The nose, chin and neck were also the site of similar lesions but much smaller in size. In closing the discussion Ormsby stated, "The striking characteristic in this case was the enormous number of dilated blood vessels. Telangiectatic lupus erythematosus is comparatively rare. . . . It is somewhat difficult

5. Foerster, H. R.: A Case for Diagnosis (Lupus Erythematosus, Telangiectasia), Arch. Dermat. & Syph. **15**:72 (Jan.) 1927.

6. Ormsby, O. S.: A Case for Diagnosis, Arch. Dermat. & Syph. **20**:388 (Sept.) 1929.

7. Ormsby, O. S.: Lupus Erythematosus Telangiectodes, Arch. Dermat. & Syph. **22**:189 (July) 1930.

to place the present case exactly; that is, to say whether it is the telangiectatic type of the disorder or whether the telangiectasia is a complication in an ordinary case. As the symptoms of the disease cleared under treatment with a gold compound the blood vessels also disappeared. This seems to show that they were involved by a common process."

Michelson's [8] case of lupus erythematosus of the telangiectatic type presented before the Minnesota Dermatologic Society occurred in a farmer aged 21, who presented a diffuse telangiectasis of the face and neck and to a lesser extent of the hands. Erythema and atrophy were also present. The biopsy showed an atrophic epidermis, dilated superficial vessels and a slight amount of infiltration in the papillary portion of the corium. In the discussion Montgomery stated that the histologic picture supported the diagnosis. Combes' [9] case was presented before the New York Dermatologic Society. The patient, a boy aged 17, had well defined eythematous patches scattered over the face and the ears. They consisted almost entirely of fine telangiectases with central atrophy. "There was . . . no scaling and only on the nose was there . . . follicular patulance." Both ears were covered with telangiectases interspersed with atrophy. An interesting case was exhibited at the Chicago Dermatological Society by Brunsting and Nomland.[10] The patient was a girl aged 15 with the diagnosis of lupus erythematosus (telangiectatic type), epithelioma (basal cell) and hematoporphyrinuria. There was a history of sensitivity to light and an epithelioma about 5 mm. in diameter on the left side of the nose. The eruption had begun at the age of 1 year. At the time of presentation there were sharply defined red patches on the cheeks, forehead, nose and chin with no scaling, but telangiectasia could be discerned in many places. In the discussion Ormsby stated that he had observed the patient when she was 18 months old and that time had demonstrated the correctness of the diagnosis of lupus erythematosus. Montgomery said that when the patient was at the Mayo Clinic a biopsy revealed the histologic picture of subacute disseminated lupus erythematosus. Gilman's [11] case of telangiectatic lupus erythematosus was presented before the Philadelphia Dermatological Society. The patient, a man aged 27, presented on both sides of the face a blotchy reticulated telangiectasia. Atrophy, scaling and patulous follicular plugs were absent. The diagnosis was not questioned in the discussion.

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8. Michelson, H. E.: Lupus Erythematosus: Telangiectatic Type, Arch. Dermat. & Syph. **22**:530-531 (Sept.) 1930.

9. Combes, F. C.: Lupus Erythematosus (Telangiectatic Type), Arch. Dermat. & Syph. **23**:572 (March) 1931.

10. Brunsting, L. A., and Nomland, R.: Lupus Erythematosus (Telangiectatic Type); Epithelioma (Basal Cell); Hematoporphyria, Arch. Dermat. & Syph. **27**:1035 (June) 1933.

11. Gilman, R. L.: Telangiectatic Lupus Erythematosus, Arch. Dermat. & Syph. **38**:265 (Aug.) 1938.

An analysis of the 8 bona fide cases of lupus erythematosus telangiectodes appearing in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY in over three decades is extremely interesting. It is significant that in the description of the first observation of this variant Crocker [1] mentioned the fact that besides the telangiectatic fiery red patches on the face there was present on the extensor surfaces of the hands a patchy persistent erythema, resembling chilblains, which after involution showed atrophic scarring. Kaposi,[2] also, called attention to the deep red patches on the face with telangiectasis preceding the onset of lupus erythematosus disseminatus in his first patients with this condition. Robertson and Klauder's [4] fatal case of the disseminated type, which began as typical lupus erythematosus and later developed into widespread telangiectatic patches with the characteristic fiery red plaques on the face, first described as "erysipelas perstans faciei" by Kaposi, corroborates the observations in Kaposi's first report of cases of the disseminated type.

Among the cases previously described which can be placed in the category of the acute or subacute disseminate type are those of Foerster,[5] Robertson and Klauder [4] and Michelson.[8] The 2 cases presented by Ormsby and those shown by Combes, Gilman and Brunsting and Nomland were of the discoid variety of telangiectatic lupus erythematosus.

Ormsby's definition of the telangiectatic discoid type of lupus erythematosus clearly and accurately describes its symptoms, yet it was my privilege to observe a patient some time ago who presented a clinical picture of undoubted lupus erythematosus telangiectodes of the discoid type which differed entirely from cases previously reported.

REPORT OF A CASE

The patient, a white woman aged 42, stated that the oldest spot appeared on her nose about a year previous to her first visit. Shortly thereafter she noted an extension of the disease on her forehead and cheeks. The lesions consisted of sharply defined patches of a light to yellowish pink color, measuring 6 to 12 mm. in diameter and numbering about a dozen. They were discrete, and not confluent. A furfuraceous scaling occurred on some. Each one showed small telangiectases radiating to the periphery of each patch, where they ended abruptly. The normal skin did not present any dilated blood vessels. A thin atrophy was observed in a few of the lesions. All the patches presented the same clinical picture with only slight variations in scaling and in atrophy. Patulous follicular openings, keratotic plugs, infiltration, scarring and adherent scales were absent. The scalp was entirely free of seborrhea and presented a normal appearance. There were no lesions elsewhere than on the forehead, nose and cheeks.

The clinical picture differed so much from guttate morphea that that diagnosis was untenable. The diagnosis of lupus erythematosus telangiectodes was based on the atrophy, slight scaling, distribution, color and the presence of telangiectases, limited entirely to the lesion itself. Because of extremely small veins, intravenous aurotherapy, unfortunately, could not be used, but the patient was given weekly intramuscular injections of bismuth subsalicylate in doses of 2 grains

(0.12 Gm.) each. After a total of nineteen doses had been given there was a decided improvement of both the telangiectasis and the lesions. The patient disappeared from observation after the nineteenth injection. She consistently refused to be photographed, but she did permit a biopsy, and a histologic examination was made by Dr. Wilbert Sachs, who reported that the microscopic diagnosis was lupus erythematosus. His description follows: "In the upper layer of the cutis and also about the adnexa was a moderate focal cellular infiltration. There was some interstitial edema and definite basophilic degeneration in the upper layer of the cutis. The overlying epidermis was irregularly acanthotic; the follicles were dilated. The granular and horny layers were retained except at the edge of the section, where there was some parakeratosis. The basal cell margin was intact and there was no edema. The cellular infiltration was composed of small, round and wandering connective tissue cells. There were no epithelioid, plasma or giant cells. The elastic tissue was clumped beneath the epidermis.

In a discussion of a paper by Goeckerman and Montgomery [12] entitled "Lupus Erythematosus: An Evaluatoin of Histopathologic Examinations," read before this association in June 1931, the late Dr. David L. Satenstein stated, "My conception is that lupus erythematosus discoides is a chronic, for a variable time an acute, inflammatory process terminating in atrophy; . . . that the atrophy is preceded by basophilic degeneration and disappearance of the elastic fibers; that without the degeneration a histologic diagnosis of lupus erythematosus discoides is not possible. Again, in those cases in which the epidermis is clinically not involved, and in which there is no scale or plug formation or hyperkeratosis, the basophilic degeneration is often the important factor in the diagnosis. . . . I base my findings on a study of more than 100 cases of lupus erythematosus of the fixed type; without the basophilic degeneration, I do not make a diagnosis of lupus erythemattosus discoides." I quote this statement of Satenstein's in full because his description of the characteristic microscopic picture in lupus erythematosus coincides with Sachs's observations in the case now under discussion. Dr. Weidman kindly examined a section and wrote that the reaction in it was compatible with lupus erythematosus, but that he was not able to make that diagnosis from the section alone, but that this might be due to the fact that the section might not have included the typical and representative part of the lesion. I do not know whether or not the section sent Dr. Weidman was the same one on which Dr. Sachs's conclusions were based.

COMMENT

From the analysis and study of previous reports of cases, even though so few in number, one can arrive at certain conclusions based on the known facts of this variant of lupus erythematosus, namely, that the

12. Goeckerman, W. H., and Montgomery, H.: Lupus Erythematosus: An Evaluation of Histopathological Examinations, Arch. Dermat. & Syph. **25**:304-314 (Feb.) 1932.

telangiectatic type of lupus erythematosus, though extremely rare, is a definite clinical variant and that it appears in the acute or subacute disseminate type as well as in the discoid type. That the telangiectasis is a part of the clinical picture is proved by its disappearance with the rest of the lesions after aurotherapy. Whether or not the variant now presented by me for the first time will find its place in the literature depends on future observers; because of the rarity of the condition it might take a long period of time.

1364 North Avenue.

ABSTRACT OF DISCUSSION

Dr. Oliver S. Ormsby, Chicago: I appreciate the paper of Dr. Bechet. It has called to attention a symptom complex which I believe is a variety of lupus erythematosus and is a distinct entity. In addition to the cases on record, I have seen a number of instances in private practice, and so I am sure that there is such an entity.

In the acute disseminated cases with telangiectasia, the telangiectasia appears to be more or less a secondary manifestation, and whether it should be called lupus erythematosus telangiectodes is a question. I have classed the telangiectatic variety with the discoid type, in which the face is largely the site of occurrence.

The case reported by Klauder (Arch. Dermat. & Syph., **8**:487, 1923) in which telangiectasia later developed, illustrates the generalized form of the disease. Klauder believed this to be a representative telangiectatic form of disseminated lupus erythematosus.

The first case of lupus erythematosus which became disseminated was the case of Kaposi which has been cited. In a few of the cases of the disseminated type, telangiectasia has occurred as a complication, which shows that telangiectasia can be a part of the process. However, as I stated before, I believe that the term lupus erythematosus telangiectodes should be limited to the type that occurs on the face and on the neck and really belongs to the discoid group.

Dr. Bechet has made an admirable presentation of a rare form of lupus erythematosus, and I am sure that many more cases will be observed now that attention has been focused on this subject.

Dr. Fred D. Weidman, Philadelphia: Not that it means anything in the cure of the disease and probably not that it means much cosmetically in the case, but perhaps mainly for testing the value of the drug, I would like to mention rutin. It is employed in patients with high blood pressure. At a recent meeting of the Philadelphia Dermatological Society (to be reported in Arch. Dermat. & Syph.) Dr. Klauder reported that the nosebleed in his patient had ceased after administration of rutin. It might be useful in dermatoses associated with telangiectasis and with purpuric hemorrhage.

Dr. Paul E. Bechet, Elizabeth, N. J.: I have nothing to add, Mr. President, other than to thank you and Dr. Ormsby for the discussion.

HYPERSENSITIVITY TO SULFAPYRIDINE

Report of a Case

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THERE are few drugs to which some patient has not shown an idiosyncrasy or allergic hypersensitivity. The sulfonamide drugs have been notable as producers of hypersensitivity, and the literature contains numerous reports of such untoward reactions. It is well known that patients may manifest their hypersensitivity to these drugs by such reactions as various types of cutaneous eruptions, pruritus, angioneurotic edema, depression of red and white blood cell counts and granulocytopenia with angina.

It has been reported that therapeutic or prophylactic desensitization, or more correctly hyposensitization, may at times be effected, but this cannot always be accomplished. The following case report represents an instance of a high degree of hypersensitivity to sulfapyridine and sulfathiazole.

REPORT OF A CASE

R. D., a 28 year old white married woman, was admitted to the New York Skin and Cancer Unit of the New York Post-Graduate Medical School Hospital on Aug. 16, 1946, for the diagnosis and treatment of a generalized pustular cutaneous eruption.

History.—Three years before admission, in the third month of her first pregnancy, the patient had a few isolated pustules on the thoracic wall. There was rapid dissemination, so that in a few days the entire body, exclusive of the head and neck, was involved. The eruption persisted unchanged until three months postpartum, at which time it began to subside. Residual lesions remained on the lower aspects of the legs, soles, dorsa of both feet, and nail beds of the fingers and toes. The nails had been shed early in the course of the disease and never grew again.

In the first month of the second pregnancy, approximately one year later, there was an exacerbation of the eruption, but this was less extensive than the first attack. This continued at its height until two weeks before term, when the lesions cleared again, with the exception of those on the lower two thirds of the left leg and the nail beds of the fingers and toes. Four days postpartum the patient received penicillin to combat the residual lesions. Seven days after the start of penicillin therapy an acute and generalized exacerbation of the eruption occurred, accompanied with chills and fever. With the exception of the residual lesions previously mentioned, this subsided in six weeks with the local use of boric acid

*From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology (Director, Dr. Marion B. Sulzberger), New York Post-Graduate Medical School and Hospital.

ointment. The residual lesions remained unchanged and quiescent for approximately one year. Two weeks before her admission 0.5 Gm. of sulfapyridine, four times daily, was administered. On the seventh day following the institution of this medication, the patient's eruption became generalized and involved the entire skin exclusive of the scalp.

Observations on Admission.—Physical examination revealed a poorly nourished white woman, not appearing acutely ill. Examination of the head and neck showed no abnormalities except for the presence of an upper artificial denture and several retained roots in the upper and lower jaws. The scalp showed a mild seborrheic scaling. The heart, lungs and abdominal viscera were normal. The blood pressure was 114 systolic and 76 diastolic. The extremities except for the lesions of the skin were normal.

The urine was normal. The blood cell count showed 4,130,000 erythrocytes, 12 Gm. (72 per cent) hemoglobin and 13,250 leukocytes, with a differential count of 75 per cent polymorphonuclear cells, 20 per cent lymphocytes and 5 per cent monocytes. The sedimentation rate (Westergren) was 74 mm. in one hour. Reactions to complement fixation and Kahn precipitation tests were negative.

The skin of the entire body was involved in a polymorphous eruption. The face was covered with a diffuse morbiliform erythema. The neck, trunk and upper and lower extremities presented a great number of scaly crusted pustules on an erythematous base. All finger and toe nails were absent, and the nail beds encrusted.

Material obtained from the pustules was placed on different mediums and attempts made to culture micro-organisms aerobically, anaerobically and under reduced oxygen tension. All cultures remained sterile. No abnormalities were observed when the material was studied for the presence of fungi and viruses.

Diagnosis, Course and Treatment.—A definitive diagnosis was not made: impetigo herpetiformis and acrodermatitis continua of Hallopeau were considered as the most likely diagnoses. The treatment consisted of a wide variety of medications, systemic and topical, without notable improvement. Streptomycin, given orally and parenterally, dihydrotachysterol ("hytakerol"), chorionic gonadotropin, estrogenic hormone, bismuth subsalicylate in oil, bismuth sodium triglycollamate ("bistrimate"), carbarsone, para-aminobenzoic acid, artificial fever therapy, vitamins and the extraction of retained dental roots were among the many therapeutic measures which failed to exert a favorable influence on the course of the disease.

Reactions to Sulfonamide Drugs.—On November 1, the patient received 1.0 Gm. of sulfapyridine with equal amounts of sodium bicarbonate every four hours. After three doses (3.0 Gm.) it was necessary to discontinue the drug because of the severe reaction. There was intense erythema of the face with edema of the upper lip, nose, eyelids and temples, and diffuse erythema of the rest of the body. In addition to an increase in the number and size of the pustules in the sites formerly involved (legs and feet), there were numerous lakes of pus measuring 3 to 4 cm. in diameter, scattered over the trunk. The patient appeared acutely ill and remained so for three days, with a temperature elevation ranging between 100.2 and 104.4 F. and a pulse rate of 110 to 160. On a regimen of diphenhydramine hydrochloride ("benadryl hydrochloride") 50 mg. every four hours and topical applications of calamine emulsion and wet dressings, this acute episode subsided within six days of its onset.

Since it was thought that this acute exacerbation was a manifestation of hypersensitivity to sulfapyridine, an attempt was then made to desensitize the patient. On November 13, after the administration of 5 mg. (0.005 Gm.) of sulfapyridine, the patient complained of slight itching of the skin and erythema of the trunk.

There was a mild exacerbation of the pustules on the legs and feet, but no febrile response. Repetition of the same dose the following day produced a similar reaction.

On November 20, 1 mg. (0.001 Gm.) of sulfapyridine was administered and the patient was observed closely for manifestations of hypersensitivity. Two and one-half hours after ingestion the patient experienced itching of the forearms, which was followed by erythema. One hour later (at three and one-half hours) erythema appeared on the neck and trunk; two and one-half hours later (six hours after ingestion of sulfapyridine) the posterior aspects of both thighs were similarly involved, with erythema of the face three hours later. Determinations of sulfapyridine levels in the blood were made on specimens drawn hourly for four successive hours after ingestion of the drug. Sulfapyridine was not detected in any of the specimens. On the following day (November 21) the erythema subsided somewhat, but new pustules appeared on the arms and trunk, while those on the left foot seemed to be undergoing involution. On November 22 (two days after the administration of the 1 mg. test dose) there was complete disappearance of the erythema and drying of the pustules, indicating a remission of the reaction.

From the foregoing observations it was concluded that the patient had a great degree of hypersensitivity to sulfapyridine and that hyposensitization was not feasible. In the attempt to determine whether there was a similar hypersensitivity to other members of the sulfonamide drug group, the patient was given 15 mg. (0.15 Gm.) of sulfathiazole on November 29, at a time when the original eruption was in a quiescent state. Three hours later a pricking sensation of the back and arms was noted, which in the course of the next three hours was followed by erythema of the trunk and upper extremities. This was not accompanied with fever or new pustules. The blood cell count at this time showed no essential change from that found on admission. There were 4,050,000 erythrocytes, 11.8 Gm. (71 per cent) of hemoglobin and 13,750 leukocytes, with a differential count of 80 per cent polymorphonuclear cells, 1 per cent eosinophils, 15 per cent lymphocytes and 4 per cent monocytes.

In view of this additional evidence of the patient's intolerance to the sulfonamide drugs, attempts at treatment with this group of drugs were abandoned.

COMMENT

According to the criteria set down by Sulzberger,[1] the condition in the case presented here falls into the class of an allergic eruption due to drugs, as a result of extreme hypersensitivity to sulfapyridine. In this connection it is particularly worthy of note that there was a seven day incubation period before the explosive outbreak following the first administration of a sulfonamide drug. After the sensitization had been established, the subsequent reactions occurred within a few hours after the administration of minute amounts of the drug. In contrast to these observations of chronologic intervals characteristic of allergic sensitizations, reactions were noted within twenty-four hours in patients

1. Sulzberger, M. B.: Dermatologic Allergy, Springfield, Ill., Charles C Thomas, Publisher, 1940, p. 38.

receiving sulfonamide drugs for the first time in the 3 cases reported by Carpenter and Gorsuch [2] as bacterids which flared up after the administration of the drugs.

It is conceivable that the present case is an instance of aggravation of a "bacterid" by sulfapyridine. However, it is unlikely that 1 mg. of the drug, diluted and distributed throughout the body, could have sufficient bacteriostatic or bacteriocidal action to release sufficient bacterial substances to produce the severe generalized reactions. Herxheimer-like reactions may well occur in some cases, but in the case herein presented this could not be expected since the doses of the sulfonamide drugs were so far below the usual therapeutic levels.

SUMMARY

A case of extreme hypersensitivity to sulfapyridine is presented. A similar intolerance to sulfathiazole in the same patient was demonstrated. Several possible mechanisms of the reactions noted are discussed, and the conclusion is reached that specific allergic sensitization is the most probable.

2. Carpenter, C. C., and Gorsuch, L. P.: Bacterids Provoked by Internal Sulfonamide Administration, U. S. Nav. M. Bull. **44**:681, 1945.

LICHEN PLANUS PEMPHIGOIDES

Report of a Case and Discussion of the Literature

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ERUPTIONS of lichen planus associated with vesicles, although not common, are not a great rarity. The vesicles may be few and scattered and of small size, or there may be multiple crops of vesicles and even large bullae. Reports of this form of eruption have appeared in the literature since 1881 when Baker (Crocker [1]) was credited as having first described such a complication of lichen planus. Kaposi [2] has been generally credited with the origin of the term lichen ruber pemphigoides and with the first description of an extensive bullous eruption occurring in lichen planus. Kaposi stated that while he had seen lichen planus associated with pea-sized vesicles, he had never previously seen large bullae in lichen planus. He apparently coined the term lichen ruber pemphigoides to segregate this eruption of bullous lichen planus from the commoner vesicular lichen planus.

The term lichen ruber pemphigoides, or lichen planus pemphigoides, has been used somewhat loosely, in that some of the dermatoses described under this term showed little resemblance to pemphigus but were actually severer degrees of the vesicular manifestation. Other cases described under this title, in which there were multiple large bullae and mild to severe constitutional symptoms, were really pemphigus-like. In some cases the bullous eruption so dominated the clinical picture that the observers of such cases wondered whether they were not dealing with two disease entities, i.e., pemphigus and lichen planus, occurring simultaneously. Kaposi [2] recorded this uncertainty, as did others.[3]

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology, New York Post-Graduate Medical School and Hospital (Dr. Marion B. Sulzberger, Director).

1. Crocker, H. R.: Lichen Planus: Its Variations, Relations and Imitations, Brit. J. Dermat. **12**:428 (Dec.) 1900.

2. Kaposi, M.: Lichen ruber pemphigoides, Arch. f. Dermat. u. Syph. **24**:344, 1892.

3. (*a*) Pautrier, L. M.: Lichen plan compliqué d'éruption bulleuse (association de lichen plan et de dermatite polymorphe de Dühring-Brocq? ou lichen ruber pemphigoïde?), Bull. Soc. franç. de dermat. et syph (Réunion dermat.) **40**:1137, 1933. (*b*) Senear, F. E., in discussion on Stillians, A. W.: Lichen Planus, Arch. Dermat. & Syph. **22**:345 (Aug.) 1930. (*c*) Zugerman, I., and Gross, P. P.: Bullous Lichen Planus with Recovery Following Use of Estrogenic Hormone, Pennsylvania M. J. **47**:571 (March) 1944.

Finger [4] and Schriener [5] suggested that bullous and vesicular lichen planus be divided into two groups. The first should include lichen planus in which vesicle formation was not extensive, of short duration and thus of little moment. The other group should consist of cases in which formation of bullae was extensive and the dominant feature. Schriener also specified that in order to be included in the latter group, vesicles and bullae should be present on skin uninvolved with lichen planus papules as well as on the papules. Pautrier,[6] in discussing the subject of bullous lichen planus in "Nouvelle Practique Dermatologique," distinguished between the two types. From a review of the cases of bullous lichen planus described in the literature, it appears that vesicle and bulla formation may vary considerably in degree and that cases have been recorded which represent transitions between the two suggested groups. In a complete review of the subject Straus [7] avoided this division and discussed the whole subject under the title "Vesicular and Bullous Lichen Planus." However, the severer types of bullous lichen planus have a fairly definite course and usually present unique features and therefore seem worthy of some segregation as suggested by the older authors.

REPORT OF A CASE

J. S., a 49 year old white man, whose occupation was that of a business executive, was a private patient of Dr. Marion B. Sulzberger, who has authorized me to publish this report. Fifteen years prior to hospital admission the patient had noticed a single lesion on the dorsum of his hand. After a clinical diagnosis of lichen planus had been made, low voltage roentgen therapy produced rapid involution of this early lesion. The same sort of eruption appeared five years later and disappeared spontaneously shortly thereafter. In January 1947 a second recurrence was manifested by lesions on the dorsa of the hands and on the forearms and legs. Examination at this time showed typical lichen planus papules on the areas mentioned. Administration of "bistrimate" (sodium bismuth triglycollamate) (Carroll Dunham Smith Pharmacal Co.) 6 tablets daily (450 mg. of elemental bismuth daily) was begun on January 27 and was continued somewhat irregularly over a period of seven weeks. The eruption spread to the thighs and upper portions of the arms during the treatment. Therefore, on March 13 the bistrimate was discontinued and arsenical therapy was started. A solution containing 2 per cent of arsenic trioxide and 1 per cent phenol in distilled water was given subcutaneously in graduated daily doses, beginning with 0.1 cc. and increasing 0.1 cc. daily. After the eighth injection, when a total of 0.036 Gm. of arsenic trioxide, or 0.0273 Gm. of metallic arsenic, had been given, the arsenic solution was discontinued because a low grade

4. Finger, E.: Ueber Lichen ruber pemphigoides, Wien. med. Wchnschr. **54**:157 (March) 1904.

5. Schriener, K.: Lichen ruber pemphigoides, Arch. f. Dermat. u. Syph. **161**:647 (Aug.) 1930.

6. Pautrier, L. M.: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936, vol. 8, p. 458.

7. Straus, M. J.: Vesicular and Bullous Lichen Planus, Acta dermat. venereol. **14**:447 (Dec.) 1933.

fever and edema of the lower legs suddenly developed. The lichen planus eruption continued to advance rapidly, and scattered papules and erythematous areas soon involved all parts of the body surface except the face. The lesions itched severely. 2, 3 dimercaptopropanol (BAL) therapy was initiated on March 29, and the patient received a total of 3.0 Gm. in seven days. On April 2 a few scattered vesicles appeared on the legs. The eruption continued to become worse, and on April 7 the patient was admitted to the hospital. The legs, feet and ankles were moderately edematous, and there was mild edema of the eyelids. The entire integument was erythematous, and there was a morbilliform papular eruption of deeper hue on the anterior and posterior aspects of the trunk. Typical lichen planus papules were present on the shoulders, ankles, anterior aspect of the chest and dorsa of the hands. The skin of the extremities was scaling mildly. On the legs there were a few scattered bullae up to 2 cm. in diameter, which were tense with clear fluid. A fine grayish reticulation typical of lichen planus was seen on the buccal mucosa. On admission the temperature was 101 F. The febrile course was remittent and gradually abated to normal in about a week. The maximum temperature was 103.4 F.

Laboratory Data.—The sedimentation rate of erythrocytes was 16 mm. per hour (Wintrobe method). The blood nonprotein nitrogen was 28.0 mg., total serum cholesterol 110.0 mg., icterus index 5.0, total serum protein 6.3 mg., serum albumin 4.4 mg. serum globulin 1.9 mg., cephalin-cholesterol flocculation plus-minus and urine urobilinogen 10.0 mg., and several urinalyses showed no deviation from normal except an occasional faint trace of albumin. The urinary excretion of arsenic was 0.08 mg. of arsenic trioxide in twenty-four hours (total quantity of urine 840.0 cc.). On April 8 the red blood cell count was 4,630,000 and the white blood cell count was 7,000, with 62 per cent polymorphonuclear leukocytes, 3 per cent eosinophils, 29 per cent lymphocytes and 6 per cent monocytes. The following day the total white blood cell count was 10,200, with 79 per cent polymorphonuclear leukocytes, 9 per cent eosinophils, 8 per cent lymphocytes and 4 per cent monocytes. A roentgenogram of the chest showed no abnormalities.

From April 10 through April 15 the patient received daily plasma transfusions of 250 cc. each. General supportive therapy was given, with mild local applications.

The erythema and morbilliform eruption gradually faded, and the edema slowly receded. The eruption of lichen planus papules became more or less generalized during the hospital stay. No new vesicles or bullae appeared, and the old ones healed. On April 21 the patient was discharged from the hospital.

The patient's general sense of well-being and energy gradually improved during his convalescence. He partly resumed his daily routine, but never returned to his normal activity. On about May 12 the patient observed a few bullae on the lower portions of the legs, which he described as ranging in size from that of a silver quarter to a half-dollar. During the next few days split-pea-sized vesicles appeared on the thighs, penis, forearms and face and in the mouth. After discharge from the hospital until the appearance of the new outbreak of vesicles and bullae, the patient had received no internal medication other than vitamin concentrates, yeast tablets and diphenhydramine hydrochloride ("benadryl hydrochloride").

The patient was readmitted to the hospital on May 28. At that time there were typical papules of lichen planus thickly distributed in plaques and scattered single lesions over the trunk, extremities and neck. The buccal mucosa displayed typical reticulated lesions of lichen planus. On the nose, chin, right elbow, umbilicus and fingers were fairly tense split-pea-sized vesicles with moderately thick walls. On the legs and feet were great bullae, ranging up to 5 cm. in diameter. Most of the bullae contained clear fluid, but in some the contents were cloudy yellow. The

temperature was normal on admission, but an intermittent low grade fever began June 10 and continued throughout the remainder of his hospital stay. Daily peaks averaged 101.2 F.

Laboratory Data.—The erythrocyte count ranged from 3,900,000 to 4,900,000, and the total leukocyte count varied from 8,650 to 13,550. The first differential count revealed 7 per cent eosinophils. This rose to a maximum of 31 per cent on June 24 and then receded to 15 per cent on the last differential count made. The

Fig. 1.—Photograph of the patient, J. S., showing extensive eruption with many ruptured bullae, pronounced hyperpigmentation and circumscribed depigmentations.

various differential counts were not remarkable otherwise. On June 4 the sedimentation rate of erythrocytes was 25 mm. per hour (Wintrobe method). Eight urinalyses revealed nothing unusual. Aerobic and anaerobic cultures from the bullae remained sterile. On June 5 the total serum protein was 8.4 mg., with the serum albumin 5.0 and serum globulin 3.4 mg. The results of other laboratory tests made on the blood serum were as follows: cholesterol, 175 mg.; calcium,

11.3 mg.; inorganic phosphates, 3.7 mg., and alkaline phosphatase, 2.0 Bodansky units per hundred cubic centimeters. Plasma carbon dioxide-combining power was 52.2 volumes per cent and the plasma chlorides were 620 mg. per hundred cubic centimeters. Smear of blister fluid displayed 4 per cent eosinophilic cells.

Fig. 2.—Photograph showing very extensive and characteristic eruption on back, buttocks and extremities.

New crops of vesicles appeared almost daily. They were usually preceded by attacks of severe itching, and there was a distinct tendency for the bullae to erupt in large groups. They appeared on plaques of lichen planus, on individual papular lesions and also on apparently normal skin. All parts of the body surface were involved intermittently except the back. Vesicles frequently appeared on the eyelids

and about the alae nasi. Vesicles formed on the mucous membranes of the nose, mouth and pharynx. From time to time the patient coughed up blood-tinged sputum and shreds of tissue. He had intermittent hoarseness of varying degrees. No blood was ever observed in the urine or stools. The conjunctivas were never involved. Bullae were especially large on the thighs, the lower aspect of the legs and on the feet. In these locations they were frequently 3 or 4 cm. in diameter. These blisters were not easily ruptured. After rupture an oozing erythematous base appeared which healed with less pigmentation than the surrounding skin and with a tendency to slight fungation and definite elevation above the adjacent skin.

Nikolsky's sign was positive on all areas of skin tested and throughout the entire period of the severe eruption.

At this time Dr. Warfield T. Longcope of Johns Hopkins Medical School saw the patient in consultation with Dr. Sulzberger. Because of the possibility that a

Fig. 3.—Close-up of abdomen and chest of the patient, J. S., showing vesicles, bullae, crusts and hyperpigmentation together with scattered depigmented and slightly elevated lesions at sites of old bullae.

remaining reservoir of arsenic might conceivably be responsible for the continuing bullous eruption, Dr. Sulzberger and Dr. Longcope agreed to administer BAL in oil once again. Two doses of BAL of 2 mg. per kilogram of body weight were given four hours apart. After the second dose the patient had an attack of severe itching. Eight hours after the second dose, a third dose was given, and two hours later another episode of severe itching occurred. BAL therapy was then discontinued. Before BAL therapy the quantities of arsenic in twenty-four hour urine specimens were as follows: 0.02 mg. as arsenic trioxide on May 31 and none on June 2 and June 6. (Normal excretion is less than 1.0 mg. of arsenic as arsenic trioxide in twenty-four hours on an unrestricted diet.) The three doses of BAL were given on June 7. The twenty-four hour urine specimen on that day analyzed for arsenic revealed 0.07 mg. of arsenic trioxide. The following results were

obtained on twenty-four hour specimens analyzed for arsenic on subsequent days: June 8, 0.03 mg.; June 9, none; June 10, none; June 11, 0.06 mg.; June 13, none; June 16, none; June 18, 0.2 mg., and June 20 and 23, none. Estimations of blood arsenic levels were made by Dr. Alexander O. Gettler, professor of toxicology at the Medical College of New York University, with the following observations: 5.0 micrograms of arsenic (element) in 100 cc. of blood on a specimen collected on June 19. (Normal range is 20.0 micrograms [0.020 mg.] or less in 100 cc. of blood.)

The reactions to the Pels-Macht test and the Macht-Astro test (phytopharmacologic tests) were negative for pemphigus on July 1.

A biopsy specimen was taken from the anterior aspect of the chest on June 2. The tissue included a vesicle which had arisen on apparently normal skin and an

Fig. 4.—Photograph showing detail of depigmented and slightly elevated sites of old ruptured bullae, with surrounding lichenification and hyperpigmentation.

adjacent lichen planus papule. The histologic studies were made by Dr. Charles F. Sims, and his report was as follows:

The epidermis was flattened throughout a good part of the section and appeared to be separated from the underlying corium in the affected zone. There was a subepidermic bulla filled for the most part with fibrin and red blood cells, a few polymorphonuclear and small round cells and occasional eosinophils. The papillary bodies appeared fairly intact, and there was a diffuse cellular reaction in the papillary and subpapillary zones, composed of small round wandering connective tissue and occasional polymorphonuclear cells. Some scattered chromatophores were visible. The infiltration formed a more or less bandlike arrangement. The vessels of the upper part of the corium were dilated and surrounded by sparse cellular infiltration similar to that previously described. The microscopic diagnosis was lichen planus bullosus.

Although extremely itchy, in great suffering and very depressed, the patient at no time appeared to be dangerously ill. Except for the skin and mucous membranes, his general condition seemed good during his entire hospital stay. His appetite was fair, and during his sixty-five days in the hospital he lost only 8 pounds (3.6 Kg.). He was allowed bathroom privileges at all times.

The following medications seemed to have no effect on the course of the disease: penicillin, 100,000 units by mouth every three hours for eleven days; sulfapyridine, 6 Gm. daily for two days; streptomycin, 0.5 Gm. every six hours for eight days; desoxycorticosterone in oil, 5 mg. daily for forty-one days; mixed tocopherol, 300 mg. daily for forty-three days, and sodium paraminobenzoate, 16 Gm. daily for eight days.

On July 24, therapy with suramin sodium ("naphuride sodium," Winthrop-Stearns, Inc.), was initiated. The first day he received 0.1 Gm., the second day 0.2 Gm. and 0.3 Gm. was given on the third day. A dose of 0.3 Gm. of suramin sodium was given three times weekly thereafter. After the third dose the crops of bullae were less extensive, and the individual bullae were smaller. The lichen planus papules also faded considerably, leaving brownish pigmented areas at their sites. Where bullae had healed recently, there were slightly elevated areas with less pigment than the surrounding skin. The patient improved generally and was discharged from the hospital on July 31.

Following discharge from the hospital the patient continued to show slow improvement. The vesicles and bullae continued to decrease in number and size. In the middle of August 1947 the patient had several large bullae on the legs; these lesions made their appearance over a period of two weeks and then healed. Small crops of vesicles appeared at infrequent intervals. By the middle of October 1947 all vesicles had disappeared, and afterward no new ones formed. Typical lichen planus lesions were widespread at the end of 1947; however, these too disappeared gradually. The hyperpigmentations slowly paled and the pruritus diminished. At the present writing (February 1948) the skin is essentially normal except for a very slight residual mottled hyperpigmentation on the thighs, arms and trunk. The patient is apparently entirely well and following his normal business, social and family activities.

COMMENT

In cases of vesicular and bullous lichen planus which have had previous arsenical therapy, the question always arises as to whether or not the bullae or vesicles are evidence of a reaction to arsenic. In 1902 Whitfield [8] reviewed this aspect of the problem and listed several reports of bullous or vesicular lichen planus which had no arsenical therapy prior to the appearance of vesicles or bullae. There are other reports in the literature of this dermatosis in patients who had received no preceding arsenical medication.[9] In some cases arsenic had been given while

8. Whitfield, A.: A Note on the Occurrence of Bullae in Lichen Planus, Brit. J. Dermat. **14**:161 (May) 1902.

9. (*a*) Crocker.[1] (*b*) Schriener.[5] (*c*) Golay, J.: La lichen plan bulleux, Ann. de dermat. et syph. **8**:543 (Oct.) 1927. (*d*) Wise, F., and Eller, J. J.: Bullous Eruptions in Hemorrhagic Sarcoma of Kaposi and in Lichen Planus, Arch. Dermat. & Syph. **7**:625 (May) 1923. (*e*) Hallopeau, H., and Lemierre, G.: Sur un lichen plan aigu avec production de bulles et desquamation furfuracée, Bull. Soc. franç. de dermat. et syph. **12**:77, 1901. (*f*) Grüneberg, T.: Lichen ruber pemphigoides bzw. bullosus und Blasenbildung bei Lichen ruber planus nach Arsen- und Germaninbehandlung, Dermat. Wchnschr. **109**:1239 (Oct. 28) 1939. (*g*) Miller, J. W.: A Case of Lichen Planus Bullosus, J. Cutan. Dis. **29**:332 (July) 1911.

the bullous or vesicular eruption was present, with apparent improvement. In still other cases arsenic had been given after the bullae or vesicles had subsided with no recurrence of these lesions.

In the case herein reported, the first bullous outbreak was originally interpreted as a possible reaction to arsenic. However, in view of the recurrence of the bullous eruption after an interval of freedom from bullae during which time no arsenic was given, it seems more likely that the whole picture was that of lichen planus pemphigoides. At no time during either hospital admission was the urinary arsenic excretion above the levels of normal.

Although it seems unlikely that the bullous eruption was due to arsenic, such a possibility cannot be entirely ruled out since minute quantities of a drug may produce an eruption in a person hypersensitive or allergic to that drug and since, even after cessation of new exposures to the specific allergen, an eruption due to drugs may remain and may continue to present new lesions for some time.[10]

Some authors[11] have expressed the opinion that trauma resulting from scratching was responsible for the formation of bullae or vesicles. Engman[12] reported a case in which vesicles could be produced by rubbing an itching area. If nonitching areas were traumatized no bullae appeared. Allen[13] observed that in curetting lichen planus papules in 1 of his patients vesicles appeared in the lesions thus treated. Grüneberg[9f] also reported a case in which vesicles could be produced by trauma to the lichen planus papules. In other cases the patient had little or no itching, and still vesicles appeared.[14] Certainly, itching and scratching are common in most cases of lichen planus, and yet vesicles and bullae are infrequently seen in this disease. In some cases,[15] as in the case herein reported, no bullae appeared on the back. It might be surmised that pressure prevented vesicle formation, since bedridden patients are likely to lie on their backs much of the time.

As to the mechanism of the formation of bullae and vesicles, most observers have expressed the opinion that it might readily be explained by increase in size of the so-called Max Joseph's lacunas. These spaces

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10. Sulzberger, M. B.: Dermatologic Allergy, Springfield, Ill., Charles C Thomas, Publisher, 1940, p. 392.

11. Trautmann, G.: Zur Lehre des Lichen ruber pemphigoides, Dermat. Ztschr. **13**:317 (May) 1906.

12. Engman, M. F.: Report of a Case of Bullous Lichen Planus, J. Cutan. Dis. **22**:207 (May) 1904.

13. Allen, C. W.: Lichen Planus as a Vesicular or Bullous Disease, J. Cutan. & Genito-Urin. Dis. **19**:475 (Sept.) 1901.

14. Leredde, M.: Le lichen plan à forme bulleuse, Ann. de dermat. et syph. **6**:637, 1895. Trýb, A.: Lichen ruber pemphigoides, Dermat. Wchnschr. **74**:563 (June) 1922.

15. Miller.[9g] Trautmann.[11]

are subepidermic and are located in the lichen planus papule. This mechanism would not explain the occasional intraepidermic vesicle formation as described by Fordyce,[16] Whitfield,[8] Golay [9c] and Ruete [17] and as illustrated in the work by Percival, Drennan and Dodds.[18] Examples of this phenomenon are present in the slide collection at the New York Skin and Cancer Unit. Enlargement of Max Joseph's lacunas would not explain the formation of vesicles and bullae on skin not involved with the typical changes of lichen planus. Attempts at explanation of this mechanism are many and varied, but few are in agreement with others.

The improvement of the eruption following administration of suramin sodium cannot be attributed with certainty to the effects of that drug. From all reports reviewed, bullous eruptions in lichen planus were generally self limited; therefore, the seeming benefit from any drug must be analyzed with objectivity and critique. However, Grüneberg [9f] reported improvement in a case of lichen planus pemphigoides following the administration of "germanin," a German drug equivalent to the American drug, suramin sodium. Scherber [19] reported improvement in papular lichen planus following "germanin" therapy. In the case here reported, the improvement which followed suramin sodium administration was rapid and unequivocal.

From all clinical descriptions in the literature, truly bullous lichen planus or lichen planus pemphigoides seems to present a fairly characteristic clinical picture and seems to run a rather definite course. The bullous phase is preceded by an acute outbreak of widespread lichen planus, usually composed of individual scattered lesions and plaques of lichen planus papules. There may also be patches of erythema of varying size without distinct lichen planus papules. The patient may or may not have had previous attacks of lichen planus. The bullous eruption usually appears suddenly. From the first, the bullae are most numerous and are of greatest diameter on the extremities. The bullae are usually fairly thick walled and rupture with difficulty, leaving eroded bases which heal readily. The bullae usually contain clear fluid, but the fluid may be hemorrhagic or purulent. At times removal of the tops of the bullae reveals their contents to be coagulated, as in the present case. These bullae usually come in crops and are frequently preceded by severe itching of the involved areas. The lesions show a tendency to

16. Fordyce, J. A.: The Lichen Group of Skin Diseases: A Histological Study, J. Cutan. Dis. **28**:56 (April) 1910.

17. Reute, A. E.: Lichen ruber planus pemphigoides, Dermat. Ztschr. **53**:522 (April) 1928.

18. Percival, G. H.; Drennan, A. M., and Dodds, T. C.: Atlas of Histopathology of the Skin, Edinburgh, E. & S. Livingstone, Ltd., 1947, p. 97.

19. Scherber, G.: Zur Behandlung verschiediner Formen von Lichen ruber planus mit Germanin, Dermat. Wchrtschr. **98**:797 (June) 1934.

grouping. Vesicular lesions have been reported in the mouth, the pharynx, the larynx and, in 2 cases, in the esophagus.[20] All these sites appeared to be affected in the case here reported. Bullae may appear on lichen planus lesions, on patches of erythema or on apparently normal skin. The diameter may range from pea to egg size or larger. Nikolsky's sign may be present or the diameter of the bullae may be observed to increase on pressure with the finger on the top of unbroken lesions. The crops of vesicles and bullae gradually decrease in size, in number of component lesions and in frequency of appearance. The lichen planus papules may show improvement before, concomitant with or following the improvement of the bullous lesions, but abatement of each manifestation is not separated by a long time interval. The bullous eruption may last from a few weeks to several months.

Pigmentation frequently appears in areas of preexisting lichen planus. It is usually brownish or sepia in hue. In some cases discoid areas of relatively less pigmentation may appear where bullae have been, and these spots may be slightly elevated. The skin usually eventually regains its normal color.

Constitutional symptoms are often present. Fever may vary from a low grade intermittent or remittent type to high remittent fever. There is usually general malaise, poor appetite, some weight loss and weakness. These symptoms are present only during the more active phase of the bullous eruption.

In a few cases minor recurrences of the bullous eruption followed within a few months, but as a general rule these did not last more than two or three weeks. No report was found of a severe and prolonged recurrence of the bullous eruption.

The most frequently used internal medication was arsenic in various forms. "Germanin" [9f] has been reported of value, and estrogenic hormone seemed beneficial in 1 case.[8c]

Reports of fatalities have been few. Pringle (Crocker [1]) reported a death in a person from a generalized exfoliative dermatitis which complicated acute bullous lichen planus. Róna [21] reported death from pneumonia of a patient with widespread lichen planus which displayed a few vesicular lesions.

SUMMARY

A case of lichen planus pemphigoides is reported and the course and observations described in detail. The common characteristics of this rare and severe variant of lichen planus are described and discussed, together with a review of the observations in previously reported cases.

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20. Zugerman and Gross.[8c] Dubois-Havenith, M.: Lichen planus de Wilson, Presse méd. belge **46**:179 (June) 1904.

21. Róna, S.: Weitere Beiträge zur Lehre des Lichen ruber, Monatsh. f. prakt. Dermat. **8**:245 (March) 1889.

VITILIGO WITH RAISED BORDERS

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AND
FRED WISE, M.D.
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WE ARE reporting a case of vitiligo with raised borders because of its rarity and unknown pathogenesis.

REPORT OF A CASE

A. L.,[1] a boy aged 12, was admitted for treatment at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Feb. 25, 1946, presenting depigmented patches of two months' duration. He had scarlet fever, measles, chickenpox and mumps during early childhood and impetigo of the face and eyebrows at the age of 7. There was dry diffuse seborrhea of the scalp but no loss of hair. The patient was sensitive about the appearance of the white patches. There were no subjective symptoms. The lesions were not preceded by tingling or itchy sensations. His general health was unimpaired.

A white spot first appeared on the penis. A similar spot developed two weeks later on the forehead; after an interval of two weeks, spots appeared on the left eyebrow and right ankle and after a lapse of another month on the left frontal region at the hair margin. The first patch on the forehead appeared as a slightly raised angry-looking reddish spot the size of a large pea. The patient applied ointment of benzoic and salicylic acid for three weeks and later tincture of iodine without result. After a period of several weeks this spot enlarged by peripheral extension and was associated with central clearing.

Dermatologic Examination.—The patient presented depigmented milky white patches on the forehead and outer side of the left eyebrow, left side of the neck, left shoulder, penis and right ankle. They varied in size from 1 to 3 cm. On the forehead were two different lesions. One was a pigmented nevus, surrounded by a zone of vitiliginous skin, situated just below the hair margin. The other was a patch of vitiligo with a raised border, below and to the left of the nevus. The pigmented nevus, present since birth, was oval shaped, dark brown, level with the surrounding skin, 2.5 by 1.5 cm., with a sharply defined paper white halo enclosing it, and measuring 0.5 cm. in width. The vitiliginous patch with the raised border was perfectly round, 2.5 cm. in diameter, completely and evenly encircled by a threadlike border, the inner surface of which was white while the outer was of the same darker color as its neighboring integument. The pigmented nevus with its halo was isolated when first seen on February 25, but the lower margin of the halo had fused with the upper margin of the vitiliginous spot beneath it when examined on June 4 (fig. 1). On the outer half of the left eyebrow, located horizontally, was an oval spot, also with a raised edge, 1.25 by 2.25 cm. There were

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1. The patient was presented before the New York Dermatological Society, March 26, 1946, by Dr. Fred Wise, on whose service the patient was treated.

a few white hairs on the outer half of the left eyebrow and vitiliginous patches without raised borders, the size of a pea to that of a finger nail, on the left side of the neck, inner surface of the left shoulder, corona and shaft of the penis and outer surface of the right ankle. The depigmented patches were not altered in texture and were not surrounded by hyperpigmented borders.

General Medical Examination.—The patient appeared to be in good health. He measured 5 feet 3½ inches (158.75 cm.) and weighed 97 pounds (44.1 Kg.). Physical examination revealed no evidence of internal disorders. The thyroid was not palpably enlarged. The pupils were moderately dilated and reacted well to light and in accommodation. The heart sounds and lungs were normal. The liver and spleen were not enlarged. The knee jerks were normal.

Laboratory Data.—The Wassermann and Kahn reactions were negative, and urine examination was normal. Blood examination showed a normal total caro-

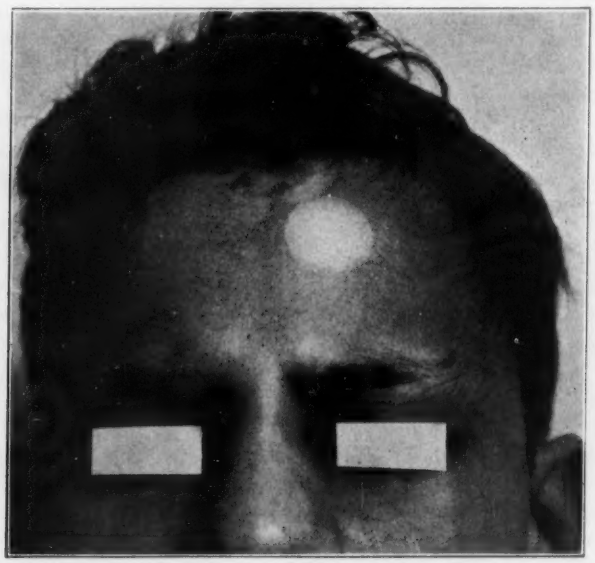

Fig. 1.—Two vitiliginous patches with raised borders, one just below the pigmented nevus and the other on the left eyebrow, the outer half of which shows whitish hairs.

tenoid content of 60 units per hundred cubic centimeters (normal 50 to 100) and a lowered vitamin A content of 5 blue units per hundred cubic centimeters (normal 10 to 20), with the Carr-Price method.[2]

Histologic Observation.—From a section taken from the lesion with the raised border on the left side of the forehead (fig. 2), Dr. Charles F. Sims gave the diagnosis of "superficial exudative inflammatory process," with the following description. The rete pegs for the most part were rather short and the papillary bodies broadened. The granular layer was intact throughout the section and composed of one to three layers of cells. The rete was rather thin, and at several parts basal cell liquefaction could be observed. At these points exocytosis were noted. In one

2. Booher, L. E.: Vitamin A in Health and Disease, in Wohl, M. G.: Dietotherapy: Clinical Application of Modern Nutrition, Philadelphia, W. B. Saunders Company, 1945, p. 225.

portion of the section there was apparently a diminution or total absence of pigment. The vessels of the upper part of the corium were moderately dilated, particularly the capillaries in the papillary bodies. Some interstitial and parenchymatous edema of the collagen in the affected zones were noted.

Under high power magnification the following observations were made. The cells were composed for the most part of small round cells, wandering connective tissue cells and some scattered chromatophores. The reaction for the most part was perivascular, except for the areas aforementioned.

Treatment.—One teaspoonful of granular brewer's yeast and 10 drops of dilute hydrochloric acid in a glass of water through a glass tube were ordered to be taken three times a day after meals. A mixture of 10 cc. of lotio neocalaminae and 20 cc. of lotio calaminae was prescribed to be used as a cover.

The patient was reexamined on June 4. At that time the raised borders of the vitiliginous patches had almost entirely regressed and were only faintly perceptible. There were no changes in the tint of the depigmented patches. More white hairs were seen on the outer half of the left eyebrow.

Examination on October 31 showed that the pigment in the nevus had almost entirely disappeared.

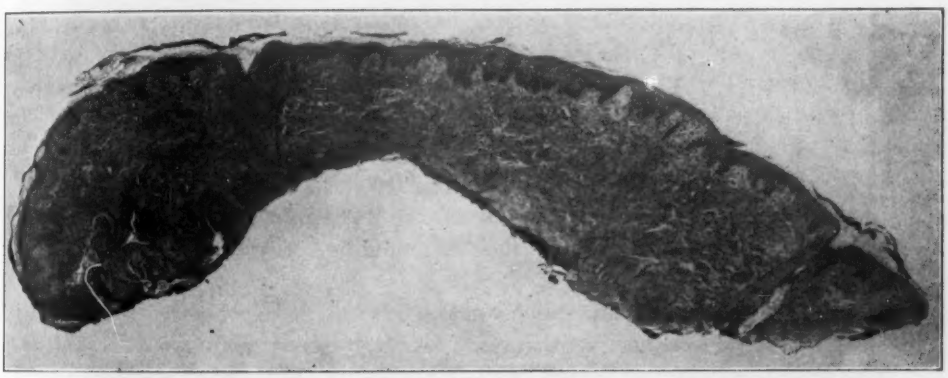

Fig. 2.—Photomicrograph of the biopsy specimen taken from the raised border, showing the perivascular superficial exudative inflammatory process (× 78).

COMMENT

Vitiliginous patches with raised borders are of rare occurrence. In review of the literature we found only 2 cases. A girl aged 10 years was presented before the Chicago Dermatological Society, October 21, 1936, by Becker and Obermayer [3] as a case for diagnosis. She had oval depigmented plaques on various parts of the body. Those on the neck showed "a slightly elevated threadlike border." Becker, in the discussion, stated, "As to the peculiar threadlike inflammatory border, we have searched through the literature and have found only 1 case in which the condition may be identical with that of this patient.[4] Some of

3. Becker, S. W., and Obermayer, M. E.: A Case for Diagnosis (Vitiligo? Atrophic Lichen Planus?), Arch. Dermat. & Syph. **36**:216 (July) 1937.

4. Habermann, R.: Paratypische Pigment-Anomalien, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 4, pt. 2.

the men who have written about vitiligo, Gans, for instance, stated that there may be a subthreshold inflammatory reaction. Gougerot said that it is always due to subinflammatory reaction, . . . but it may be that in this child there is sufficient inflammatory reaction to produce a real border." The patient was again presented on April 21, 1937,[5] before the aforementioned society, as a definite case of vitiligo.

The patient referred to in Jadassohn's Handbuch was that of Freudenthal,[6] who described a case of vitiligo associated with an elevated red border in a patient with "lues ii and iii," under the title "luetic leukomelanoderma in the form of a pseudovitiligo." The patient had seropositive syphilis. On the right lower quadrant of the abdomen were two depigmented patches, one discoid, with a diameter of about 2 inches (5 cm.), and the other ovoid, about 6 by 2 inches (15 by 5 cm.). These depigmented areas showed sharply defined slightly elevated red borders. They appeared shortly after the regression in situ of an erythematous serpiginous late syphilitic exanthem.

A case of leukoderma [6a] with inflammatory borders was presented by one of us (F. W.) before the Manhattan Dermatologic Society on May 13, 1941.[7] The patient, a woman aged 47, had leukodermic patches on the wrists, forearms and front of the neck. On the latter area the lesions were bordered by a "distinct red slightly raised finely scaled border, 2 to 3 mm. in width." She had frequently been using ammonia and scouring powder in her work as chambermaid. When the patient was seen two weeks later, the inflammatory borders had entirely regressed.

The pigmented nevus and its halo (fig. 1) could properly be called leukoderma acquisitum centrifugum, since it has in common with the condition described by Sutton,[8] and more so with the verrucous and hairy nevi surrounded by achromic zones reported by Stokes,[9] a whitish oval spot enclosing a nucleus-like primary lesion. However, in the light of the newer conception that the depigmented zone and its central lesion in some cases of Sutton's disease are component parts of a whole nevus,[10] at least the first word in the title leukoderma acquisitum centrifugum is

5. Becker, S. W., and Obermayer, M. E.: Vitiligo, Arch. Dermat. & Syph. **37**:99 (Jan.) 1938.

6. Freudenthal, W.: Lŭische Leŭkomelanodermie unter dem Bilde einer Pseudovitiligo, Arch. f. Dermat. u. Syph. **156**:142, 1928.

6a. Leukoderma is here interpreted as secondary depigmentation and vitiligo as a primary loss of pigment.

7. Wise, F.: Leukoderma with Inflammatory Border, Arch. Dermat. & Syph. **45**:218 (Jan.) 1942.

8. Sutton, R. L.: An Unusual Variety of Vitiligo (Leucoderma Acquisitum Centrifugum), J. Cutan. & Ven. Dis. **34**:797 (Nov.) 1916.

9. Stokes, J. H.: Leukoderma Acquisitum Centrifugum (Sutton), Arch. Dermat. & Syph. **7**:611 (May) 1923.

10. Feldman, S., and Lashinsky, I. M.: Halo Nevus, Leukoderma Centrifugum Acquisitum (Sutton), Leukopigmentary Nevus, Arch. Dermat. & Syph. **34**:590 (Oct.) 1936.

erroneous since in leukoderma no changes are normally found except depigmentation. Halo nevus, suggested by Feldman and Lashinsky [11] or, perhaps, nimbus nevus, would, therefore, be a more suitable term.

The superficial exudative perivascular inflammatory process with the round cell infiltration would indicate the possibility of a toxic cause for the vitiliginous patches of our patient. This conception is strengthened by the lowered vitamin A content of 5 blue units per hundred cubic centimeters of blood (normal 10 to 20), as a deficiency in vitamin A may lower the natural resistance to various bacterial infections, possibly due, as expressed by Kolmer,[12] to "some defect in the efficient functioning of the reticuloendothelial system."

The treatment was that described by Hathaway,[13] who treated 14 patients with vitiligo with 2 capsules of vitamin B complex fortified with nicotinic acid, thiamine hydrochloride and riboflavin and 10 minims (0.62 cc.) of dilute hydrochloric acid after meals. In 9 patients who cooperated, the disease cleared up in 7 and improved in 2. These patients continued the medication for one to two years, with half the dose after the patches assumed the coloration of the surrounding skin.

Hathaway raised the question as to which component or components in the vitamin B complex may be responsible for the good results achieved. This unknown factor may be para-aminobenzoic acid, as Sieve [14] reported the gradual return of pigmentation in cases of vitiligo with 100 mg. tablets of this acid administered three times a day.

SUMMARY

A patient is herein presented with vitiliginous patches, two of which, on the forehead, had distinct raised borders. Only 2 such cases have thus far been reported in literature, 1 by Becker and Obermayer and 1 by one of us (F. W.). The case reported by Freudenthal was in a patient with tertiary syphilis.

The title halo nevus rather than leukoderma acquisitum centrifugum is more suitable for the pigmented nevus and its whitish halo in our patient and for all achromic zones containing a central nevus.

The perivascular round cell infiltration and the lowered vitamin A content in the blood would suggest that the causative factor in our case may be of a toxic nature. The treatment with vitamin B complex and dilute hydrochloric acid was prescribed according to the method reported by Hathaway.

11. Feldman and Lashinsky,[10] p. 594.

12. Kolmer, J. A.: Nutrition in Relation to Infection and Immunity, in Wohl, M. G.: Dietotherapy: Clinical Application of Modern Nutrition, Philadelphia, W. B. Saunders Company, 1945, p. 521.

13. Hathaway, J. C.: Vitamin B Complex for Vitiligo, Arch. Dermat. & Syph. **52**:117 (Aug.) 1945.

14. Sieve, B. F.: Effects of a New B Complex Factor on Pigmentation and Fertility, South. Med. & Surg. **104**:135 (March) 1942.

PSORIATIC ERYTHRODERMA, EPITHELIOMATOUS CHANGES AND WARTLIKE GROWTHS

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IN 1925 Levin [1] recorded a unique instance of universal psoriasis complicated by tumor-like formations. At that time he stated the belief that these lesions resembled those described by Unna [2] (1890) as parakeratosis scutularis and by Weiss [3] (1912) as parakeratosis ostracea. The outstanding clinical feature was the presence of verrucous excrescences, varying in size from that of a lentil to that of a quarter, some pale and others pink, and occurring chiefly on the lower limbs in irregular distribution. The pathologic features reported by Levin were those of typical psoriasis, accompanied with pronounced acanthosis of a degree sufficient to explain the warty clinical appearance. The tumor-like aspect was attributed by him to a combination of swelling of the fibrous tissue, intense acanthosis and cellular infiltration in the cutis. Arsenic was eliminated as a possible cause. In 1939 Levin presented this patient again.[4] In the interim, since 1937, these nodules had increased in size and several had undergone subsequent ulceration. Levin reported that in 1934 a biopsy specimen of one of the ulcerated lesions had revealed evidence of epithelioma, probably squamous in type (pearl formation). On the other hand, a biopsy specimen removed in 1939 revealed changes that were consistent with the diagnosis of psoriasis verrucosa. In the discussion of this case Peck stated that there were at least two other biopsies which had shown only changes of typical psoriasis, one additional biopsy showing a fibroma in the cutis and still another revealing alterations that

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1. Levin, O. L.: Universal Psoriasis Complicated by Tumor-Like Formations, Arch. Dermat. & Syph. **12**:360 (Sept.) 1925.

2. Unna, P. G.: Parakeratosis Scutularis, in Unna, P. G.; Morris, M.; Duhring, L. A., and Leloir, H.: Atlas von seltener Hautkrankheiten, Hamburg, L. Voss, 1890.

3. Weiss, L.: Parakeratosis Ostracea (Scutularis), J. A. M. A. **59**:343 (Aug. 3) 1912.

4. Levin, O. L.: Erythroderma Psoriaticum with Tumor Growths (Epitheliomatous Changes), Arch. Dermat. & Syph. **41**:1180 (June) 1940.

were strongly suggestive of epithelioma. Nevertheless, Peck doubted that this patient had had a true epithelioma. However, the title of this presentation indicated that Levin regarded the epitheliomatous changes as an important part of the clinical picture.

It is apparent that the views on this subject are discordant and need further clarification. For the purpose of establishing this peculiar syndrome on a clinicopathologic basis, we are reporting additional data on the subsequent course of Levin's case, as well as another striking example of this entity.

REPORT OF A CASE

I. G., a man aged 22, was admitted to Montefiore Hospital Dec. 12, 1944, with a widespread eruption that had first appeared at the age of 2½ years in the form of red scaly areas on the tibias. At the age of 7, similar lesions were observed on the forearms, and these soon coalesced into large patches. At about this time he received medication in the form of drops by mouth, but this was stopped at the end of a week because he complained of frequent urination. Following this, he received roentgen rays to various parts of the body for a period of several months. Some time later, ultraviolet irradiation was used. In 1933 he was observed at another hospital, where a diagnosis of psoriasis was made. Subsequently, the skin on the dorsa of the hands was affected, and still later patches appeared on the trunk. About five years before our observation the skin of the entire body, for no apparent reason, became red, dry and scaly, and, at about this time, the joints of the ankles and knees became red, swollen and painful. Several months later, the articulations of the right hand were similarly affected. Although there were periods of improvement, at no time did the skin or joints return to a normal state, nor was there ever evidence of a pustular or moist component in the cutaneous lesions. Shortly before admission, the joints of the left hand became red, swollen and painful. The past history and the family history were noncontributory.

Physical examination revealed a universal, nonpruritic, erythematous and scaly eruption. On the scalp the scales were dry and silvery white. On the body the erythema was bright red, such as is commonly seen in the psoriatic process. The dorsa of the feet were diffusely covered by a similar eruption, with a sharp margin about ¾ inch (about 1.9 cm) from the soles. There were discrete areas of eruption on the soles, these patches having distinctly psoriatic attributes. There were subungual hyperkeratoses of the finger nails. In addition, the skin of the legs and left forearm showed scattered irregularly elevated rough wartlike excrescences, varying in size from that of a pinhead to that of a small pea. In particular, there were two larger wartlike lesions, one on the left forearm and the other on the left knee. The palms and soles were free of any changes that might be considered as arsenical keratoses. There was also deforming arthritis, which involved chiefly the hands and feet and to a lesser degree the knees and cervical part of the spine.

The laboratory studies (such as blood cell count, serologic test, urinalysis, determination of blood calcium and cholesterol, serum sodium and potassium, serum albumin and globulin, glucose tolerance test and basal metabolic rate) revealed no significant abnormalities. Erythrocyte sedimentation rate was somewhat more rapid than normal (21 mm. in one hour). Vitamin C saturation test showed some retention, the significance of which is unclear. At the Presbyterian Hospital (1944) an arsenic determination revealed a value of 0.07 mg. per hundred grams of dried blood, a

result considered to be within the limits of normal. Our laboratories (1946) found only a faint trace of arsenic in a twenty-four specimen of urine, a result likewise regarded as essentially normal. Roentgenograms of the various affected joints showed abnormalities which were consistent with the diagnosis of rheumatoid arthritis.

The nature of the eruption, the peculiar bright red color, the circumscription of the rash at the lower margins of the feet, the circumscribed red scaly patches on the soles, the striking subungual hyperkeratoses of the finger nails and the type of arthropathy in this young person were changes that were consistent with the diagnosis of psoriatic arthropathy and psoriatic erythroderma. Moreover, observers

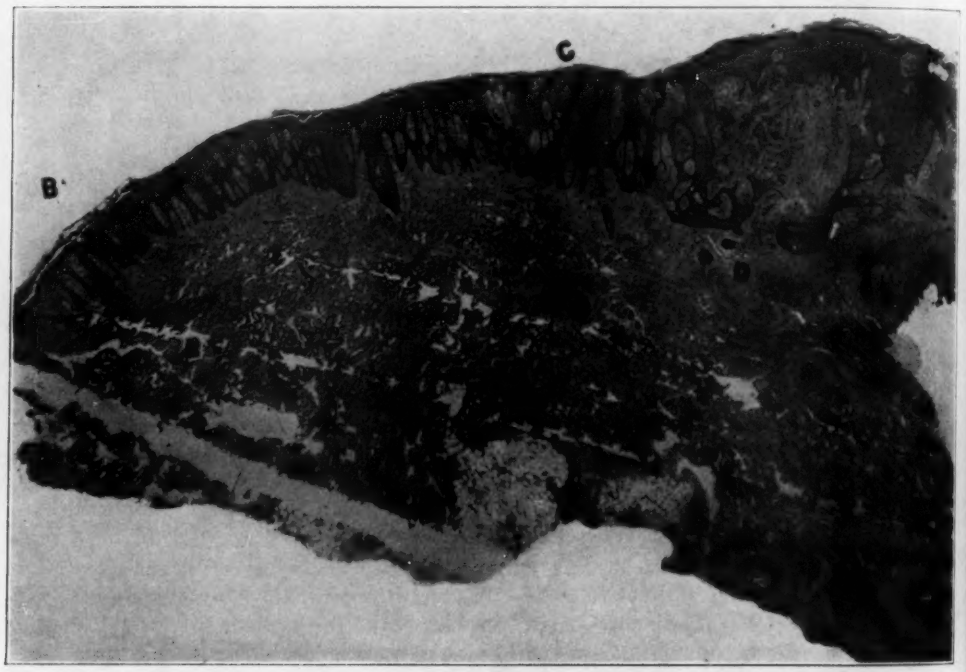

Fig. 1.—In the same section are seen an area of psoriasis (*B*), an intermediate zone with irregular and intense acanthosis, with numerous daughter peglike processes (*C*), and an area of basal cell epithelioma (*D*) (× 10).

who had seen the patient previously in the earlier stages of the disease had unanimously agreed that the eruption was a typical example of psoriasis.

The main interest in this case was centered about the peculiar warty formations on the left forearm and lower limbs, particularly since one of us had observed similar lesions in the case recorded by Levin. For this reason, the histologic studies made on these lesions will be described in detail.

Histopathologic Studies.—Biopsy A: On the extensor aspect of the left forearm, several inches above the wrist, there was a round grayish yellow wartlike lesion, about 5 mm. in diameter and elevated about 2 mm. This lesion had been first noted by the patient a few months before the present admission, and it had not grown appreciably within the period of our observation of over one year, nor had

there ever been any evidence of ulceration at any time. The growth was completely excised July 23, 1946. The psoriatic eruption on this limb had been present continuously for over ten years.

Microscopic study disclosed that the lesion was composed of three relatively distinct portions: (1) an area of typical psoriasis, (2) an intermediate zone and (3) an area showing alterations of a neoplastic nature, arising gradually from the preceding portion (fig. 1). In the part of the section showing the changes of psoriasis (fig. 2) there was acanthosis, as indicated by long fairly regular pegs. The overlying epidermis revealed many scattered areas of parakeratosis which were commonly seen in relation to the thinned out suprapapillary plates. The malpighian

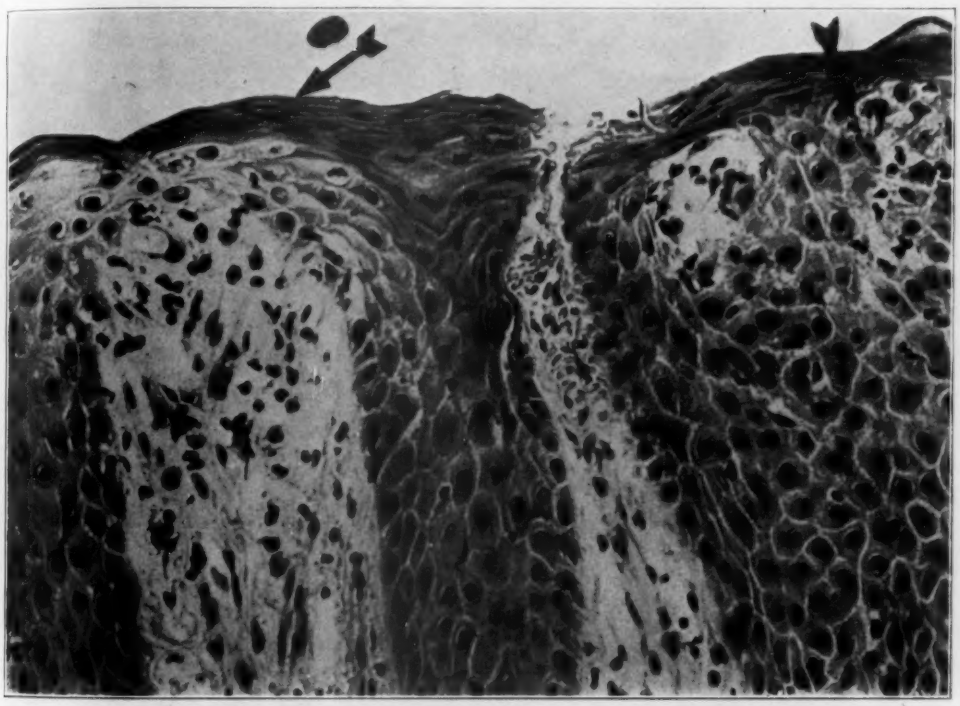

Fig. 2.—High power of area B in figure 1. Section shows the features of psoriasis. The black arrow on the left side of the photograph points to a zone of parakeratosis and thinned out suprapapillary plate. The black arrow on the opposite side points to a wandering cell in a channel-like space (description in text) (× 200).

layer was slightly edematous and revealed a moderate degree of intracellular and intercellular edema. Scattered throughout this area, particularly in the upper portion, were longitudinal narrow spaces containing deformed white blood cells in a channel-like distribution; these cells resembled sometimes polymorphonuclear leukocytes and at other times deformed mononuclear cells. No definite microabscesses were seen. The papillae were, for the most part, regularly elongated and congested and revealed a mild cellular infiltrate of nonspecific type. As one proceeded toward the neoplasm, the rete pegs became more and more elongated and irregularly distributed, with more and more daughter peglike processes. In the intermediate zone (fig. 3) the peglike processes seemed normal in appearance, except

that the corresponding subpapillary areas were sites of a relatively pronounced reactive inflammation. A point was reached where the daughter pegs began to take on the appearance of a basal cell epithelioma, as indicated by the collections of basal cells of hyperchromatic character. Finally, at one point (fig. 4)

Fig. 3.—High power of area C in figure 1. The irregular acanthosis with the daughter processes is seen. At *A*, the latter are seen as well as the diffuse reactive inflammation. The arrow points to beginning basal cell epithelioma (× 30).

there was an area in which the basal cell epithelioma seemed to be breaking through the basement membrane, and here the cells seemed to have assumed a more transitional character. The reactive inflammatory process was most pro-

nounced in that portion of the section which was of neoplastic nature. The epithelioma and its corresponding inflammatory zone did not extend below the middle portion of the cutis.

Biopsy B: The second growth (fig. 5), which was present on the front of the left knee, was similar in appearance to the one previously described, except that

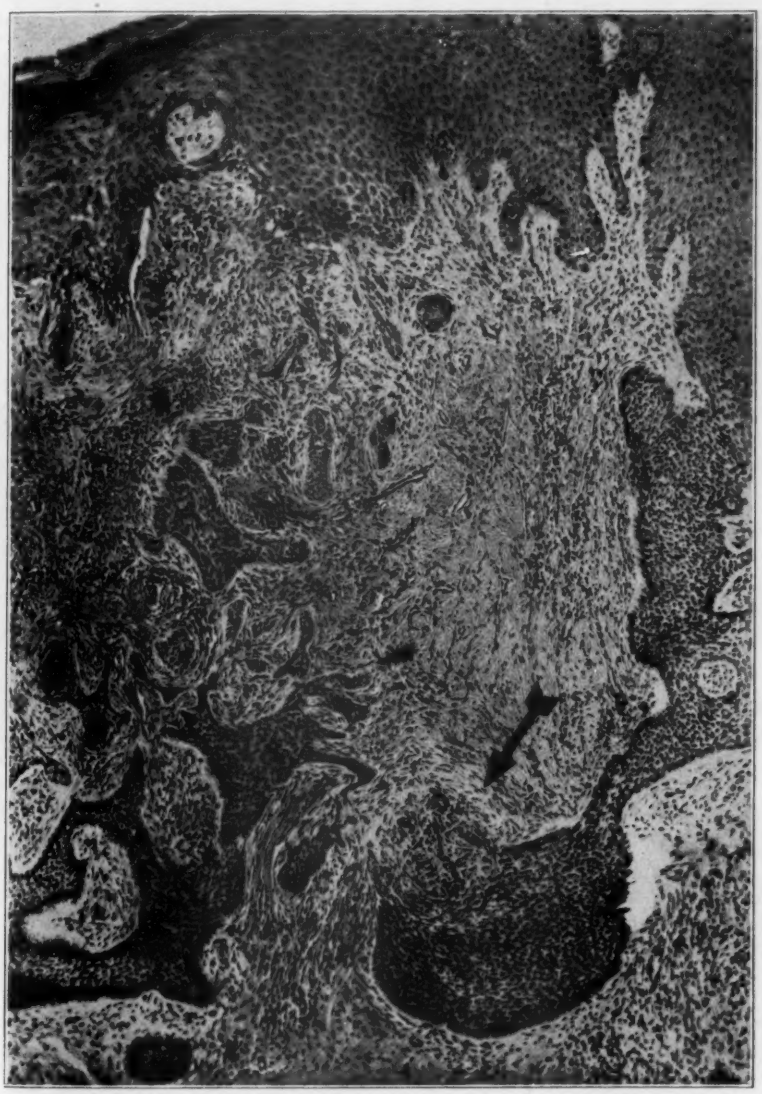

Fig. 4.—High power of area D in figure 1. An area of basal cell epithelioma. The arrow points to a portion of neoplasm that seems to be breaking through the basement membrane (× 30).

it was slightly larger (6 mm. in diameter). The patient had first noted this lesion about two years before admission. This growth was excised November 7. The eruption of psoriasis on this limb had been present more than fifteen years.

Microscopic study revealed the characteristic changes of psoriasis. To one side of the center of the section, the papillary pegs were elongated and irregular, and in one portion of the middle part of the cutis there were two or three collections of hyperchromatic cells, which, in the opinion of Dr. W. Sachs, constituted probable evidence of early basal cell epithelioma. Adjacent to this area there was a fairly

Fig. 5.—The arrow points to the growth on the area of the left knee (histopathologic studies, biopsy B, in text). In the area below the growth, there are irregular excrescences in a mild form.

well circumscribed zone in the cutis, containing many young blood vessels with scattered fibroblasts and intertwining masses of collagenous tissue. This appearance, which at first seemed to resemble that of a fibroma, was subsequently interpreted as that of granulation tissue with secondary fibrosis. In microscopic examination (magnification 10 times) the central elevation of the lesion was seen to be

due almost entirely to this mass of granulation tissue along with the area of irregular rete pegs.

Biopsy C: For purposes of comparison, a third biopsy specimen was taken from an area of uncomplicated psoriasis, situated on the lateral aspect of the left leg about 1½ inches (about 3.8 cm.) below the knee (December 24). Except for the absence of microabscesses, the section showed the characteristic features of psoriasis. The rete pegs were regularly and gracefully elongated, with a moderate amount of congestion and inflammatory reaction of nonspecific type in the papillary bodies. There was a moderate amount of intercellular and intracellular edema in the malpighian layer, and this was surmounted by a heavily parakeratotic zone. There was no evidence of a granular layer throughout this section.

Fig. 6.—Irregular acanthosis over an area of fibrosis arising on the basis of granulation tissue. The fibrotic area is set off by arrows. The vascularity of this fairly well circumscribed lesion in the cutis may be noted. (See biopsy D and compare with biopsy B.)

Biopsy D: The fourth biopsy specimen was taken from a wartlike lesion situated about ¾ inch (about 1.9 cm.) from the site of biopsy C. The growth was 2 mm. in diameter and elevated about 1 mm. above the surface. In this section (fig. 6) the features of psoriasis seemed to be masked somewhat by a pronounced irregularity in the rete pegs. In one portion of the section, near its center, there was a moderate inflammatory reaction in the subpapillary zone. Nearby, in the center of the lesion, there was an area containing collections of spindle cells and a considerable number of capillaries separated by irregular bands of fine and coarse collagenous fibers. This appearance resembled strikingly that already described in biopsy B, but differed only in its smaller size, its less circumscribed character

and its more advanced stage of organization. In microscopic examination (magnification 10 times) the elevation in this warty growth was seen to be due to the presence of this inflammatory fibrotic area together with the overlying irregularly elongated rete pegs.

COMMENT

1. *Relation Between Psoriasis and Epithelioma.*—Few observers have studied the possible relation between psoriasis and epithelioma, and the views expressed on this point have been discordant. One of the most complete analyses of this subject is that given by Alexander,[5] who collected 18 cases, mainly from the literature, in which this combination had been described. Alexander classified these cases into three groups: (*a*) 5 cases in which the epithelioma arose directly from arsenical keratoses found in patients afflicted with psoriasis, (*b*) 6 cases in which arsenic was thought to have caused a typical proliferation of psoriasis, without the intervention of arsenical keratoses, and (*c*) 7 probable instances in which isolated psoriatic lesions underwent direct carcinomatous change in the absence of such extraneous factors as arsenic. The last group was considered as analogous to carcinomas arising on areas of roentgen change, scars, lupus and the like.

It is not our intention to discuss all the possible examples in which combinations of psoriasis and epitheliomas of one type or another have been encountered. In many such instances the possibility of coincidence must be considered. In regard to Alexander's classification, we are unable to accept the sharp distinction between his first two groups on the basis of the cited case reports. There is evidence, for example, that the lesions in some of the cases in his second group were really epitheliomas occurring in areas of arsenical keratoses in unusual locations, a view that seems to be supported by the simultaneous occurrence in these cases of typical arsenical keratoses in the palms and soles. Possibly arsenic may cause atypical proliferation of epithelium in other dermatoses, and this has been postulated in the case of certain lesions, such as leukoplakia on a syphilitic background. However, Alexander's second group is based on data that are inadequate to substantiate this view, so far as psoriasis is concerned. We are also uncertain of whether all the cases grouped in Alexander's third class really belong there. Nevertheless, Alexander's report has the merit of attempting to separate examples of direct epitheliomatous changes in psoriatic lesions from the cancerous alterations caused essentially by such extraneous factors as the intake of arsenic and roentgen changes.

It is evident that, in order to establish the occurrence of direct epitheliomatous change in psoriasis, two possible complicating factors

5. Alexander, A.: Carcinomentwicklung auf psoriatischer Basis, Arch. f. Dermat. u. Syph. **129**:5, 1921 (extensive bibliography).

must be eliminated, namely, intake of arsenic and roentgen alterations. Arsenic is, of course, a factor that must always be considered in chronic dermatoses, since in such cases this medicament is apt to be given at one time or another. Whereas this is less likely to be true today, it was certainly a common occurrence a few generations ago, when most epitheliomas in patients with psoriasis arose on the basis of arsenical keratoses. In Levin's case the patient did not receive arsenic in any form.[6] Our patient took drops about twelve years before observation, but this medicament, which was probably a preparation of arsenic, was discontinued after a week because of unpleasant side effects. It seems most unlikely that this small amount of arsenic can be implicated in the presenting epitheliomatous changes. In 1944 and 1946 arsenic determinations of the blood and urine, respectively, gave results within the limits of normal. Whereas this does not exclude the possibility of previous ingestion of arsenic, these data eliminate, at least, the possibility of continued absorption of large amounts of arsenic, either from ingestion or from exposure. As far as roentgen irradiation is concerned, Levin's case may have received radiation therapy many years ago, whereas our patient received a moderate amount of roentgen irradiation. However, neither in Levin's case nor in our own could evidence be found that these peculiar wartlike lesions arose on the basis of prior roentgen change. Clinically there was no evidence of radiodermatitis in the immediate neighborhood of these lesions, and this could be further substantiated in both instances by the absence of roentgen alterations in the various biopsy specimens taken.

We believe, therefore, that in both Levin's case and in our own, the factors of arsenic and roentgen change can be eliminated with reasonable certainty as cause of the epitheliomatous alterations. The evidence favors the view that in certain instances of psoriatic erythroderma primary epitheliomatous changes may occur in such altered skin.

2. *Nature of the Wartlike Lesions.*—In studying our material we found that there were essentially two types of pathologic alterations in the wartlike lesions observed in our case. (*a*) The first type was exemplified by the changes described in biopsy A. This disclosed a zone of basal cell epithelioma in juxtaposition to an area in which there was pronounced and irregular acanthosis. (*b*) The second type was illustrated by the observations in biopsies B and D. Here the wartlike appearances were created by the combination of irregular acanthosis and an area of granulation tissue going on to fibrosis. In Levin's patient one of the biopsies showed what was considered to be

6. Levin, O. L.: Personal communication to the authors.

a fibroma. This is of interest because in our case the fibrotic granulation tissue was diagnosed at first as fibroma, an opinion which was revised when similar alterations were found in a second biopsy specimen from an area nearby. We feel that the report of fibroma in

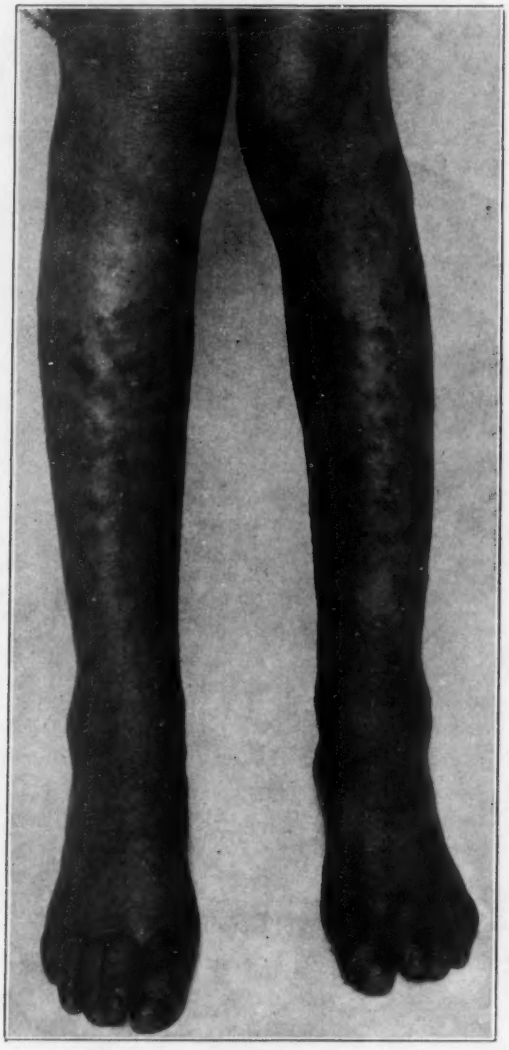

Fig. 7.—Wartlike lesions on the legs of Levin's patient. These excrescences are in an early stage.

Levin's case should be reconsidered in the light of the observations that we have reported.

The common denominator of the three biopsies, A, B and D, was the presence of intense and irregular acanthosis. In biopsy A this

irregular acanthotic zone lay next to that area which was undergoing the changes of basal cell epithelioma. It is of interest that at one point of the section the basal cell epithelioma seemed to have penetrated the basement membrane. In Levin's case the pathologic diagnoses fluctuated between epithelioma and psoriasis verrucosa, whereas one sec-

Fig. 8.—The appearances on the legs of Levin's patient in a later stage. The small excrescences have now become large wartlike growths.

tion, as stated previously, showed a "fibroma" in the cutis. It is important, therefore, to report that in Levin's patient other lesions of squamous cell carcinoma developed, with metastases ending in death. On the other hand, our patient is a young person who has had the wartlike lesions only a few years, and we are therefore, in all likelihood, observing early changes. We believe that the presence of pro-

nounced irregular acanthosis is probably a forerunner of epitheliomatous alterations in the future. Whether these will turn out to be purely basal cell or squamous cell epithelioma, we do not know.

3. *Clinicopathologic Features of the Syndrome.*—The clinicopathologic features exhibited in our case were essentially the counterpart of those shown by Levin's patient. These 2 instances of psoriatic erythroderma illustrate the developmental phases of the peculiar wartlike lesions observed in such cases (figs. 5, 7 and 8).

(*a*) Clinical Features: The wartlike growths have been encountered in young persons (our patient was 19 years old at the time of observation) who have been afflicted with extensive psoriasis for many years. At onset these lesions vary in size from that of a pinhead to that of a pea. They are a dirty grayish yellow, are elevated only a few millimeters and present a rough surface fading gradually into what seems to be ordinary psoriatic skin. Their sites of predilection are the legs, where they are irregularly distributed. On palpation there is imparted the feeling of multiple uneven excrescences. These lesions may be seen as more or less discrete growths on other parts of the body, such as the forearms and face. In the latter situation the growths may be smoother to the touch, possibly because of rubbing incidental to washing the face. At their onset the growths are nonulcerated and are apt to remain in this state for many years. They arise insidiously and grow gradually to form more elevated rough irregular plaques of variable size, some attaining the diameter of a dime, with irregular and uneven borders. After a variable period, usually measured in years, ulceration occurs in occasional lesions. Such ulceration seems to portend the occurrence of malignant change, probably squamous cell in type, as in Levin's case. It should be stressed, however, that epitheliomatous alterations may be encountered in nonulcerated growths, as in our case (basal cell epithelioma). Judging on the basis of Levin's case, the clinical course may be terminated by death because of metastases from one or more foci of squamous cell carcinoma, and, as the changes seem severest on the lower limbs, the inguinal glands are apt to be the first obvious site of a metastatic deposit. It is probable that various types and stages of epitheliomatous alteration may be seen in the later course of these cases.

Arsenic and roentgen effects can be eliminated with reasonable certainty as causative agents; the former on the basis of the clinical and laboratory observations, and the latter on the basis of the clinical features and the absence of roentgen changes in the histologic pictures.

(*b*) Pathologic Features: The various biopsies made in Levin's case showed at different times changes classified as psoriasis verrucosa,

squamous cell cancer and fibroma. Our studies revealed that these wartlike growths could be classified in at least two categories: (1) intense and irregular acanthosis shading over into basal cell epithelioma (biopsy A) and (2) intense and irregular acanthosis overlying or in relation to granulation tissue undergoing fibrosis (biopsies B and D).

SUMMARY AND CONCLUSIONS

It appears that there is a definite syndrome in which long-lasting psoriatic erythroderma is accompanied subsequently with the appearance of nonulcerated wartlike growths on various parts of the body, especially the legs. These wartlike excrescences, which may or may not be associated with peculiar fibrotic changes in the cutis, are probably forerunners of epitheliomatous changes of various types. In their future course some of these lesions may ulcerate. Thus far, squamous cell epithelioma and an active type of basal cell epithelioma have been encountered, the latter in a nonulcerated growth. Whether chronic erythrodermas, other than the psoriatic type, are capable of giving rise to these peculiar wartlike lesions is a matter which requires further observations.

Dr. H. Zimmerman, Pathologist to the Montefiore Hospital, assisted with suggestions and criticisms.

OSTEOMA CUTIS

Report of a Case

MORRIS LEIDER, M.D.
BROOKLYN

OSSIFYING processes in the skin, either primary (neoplasia) or secondary (metaplasia), are rare occurrences. The discovery of bone formation in the skin is even rarer than its occurrence, and, consequently, reports of the phenomenon are rarest of all. Ossification in other extraskeletal sites, aside from in the skin, is not too uncommon. Year after year there are several reports of bone deposit in organs like the kidneys and musculature. Prior to 1928 Hopkins [1] could find only about 5 cases, beginning with Virchow's case and including his own, of osteomas in the skin. Since then, i. e., in the past twenty years, I have been able to discover only seven more reports of the condition.[2] There must be a few cases that have not been recorded in the periodical literature, like that of Andrews, who in his textbook [3] cited an instance in which he was able to demonstrate the deposits of bone in the skin in roentgenograms made on dental film. In this dozen or so of cases some osteomas were secondary to preexisting lesions, like nevi, epitheliomas, scars and chronic inflammatory dermatoses; others were primary, i. e., arising in apparently normal loci.

The case herein reported is nearly an exact replica of Hopkins' case,[1] and both are unique in the number of osteomas recovered, their localiza-

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology, of the New York Post-Graduate Medical School and Hospital (Dr. Marion B. Sulzberger, Director).

1. Hopkins, J. G.: Multiple Miliary Osteomas of the Skin: Report of a Case, Arch. Dermat. & Syph. **18**:706 (Nov.) 1928.

2. (*a*) Dietrick, C.: Osteomatosis Cutis, Arch. Dermat. & Syph. **41**:562 (March) 1940. (*b*) Pirilä, P.: Genuine Cutaneous Osteoma: Case Report, Acta dermat.-venereol. **22**:360, 1941. (*c*) Higuti, K., and Mitumoto, S.: Formation of Bone in the Skin (Osteoidoma Cutis): Two Cases, Hihu-to-Hitunyo (Abstr. Sect.) **9**:12 (April) 1941. (*d*) Lilga, H. V., and Burns, D. C.: Osteomatosis Cutis: Report of a Case, Arch. Dermat. & Syph. **46**:872 (Dec.) 1942. (*e*) Mercadal Peyri, J., and Trallero Felez, J.: Primary Subcutaneous Osteoma, Acta dermo-sif. **35**:280 (Dec) 1943. (*f*) Vero, F.; Machacek, G. F., and Bartlett, F. H.: Disseminated Congenital Osteomas of the Skin with Subsequent Development of Myositis Ossificans: Case in an Infant, J. A. M. A. **129**:728 (Nov. 10) 1945. (*g*) Costello, M.: Metaplasia of Bone: Report of a Case, Arch. Dermat. & Syph. **56**:536 (Oct.) 1947.

3. Andrews, G. C.: Diseases of the Skin for Practitioners and Students, ed. 3, Philadelphia, W. B. Saunders Company, 1946.

tion and distribution in the face, their size and in several other respects relative to comparable data of the other cases. The table is a summary

Comparative Data in Two Cases of Osteoma Cutis

Data	Hopkins' Case	Case Described Herein
Age (yr.)	44	34
Dermatologic history	Acne of 10 years' duration, onset at 30 years; comedos; papules; pustules; scars	Acne of 21 years' duration, onset at 13 years; comedos; papules; pustules; scars
Previous dermatologic treatment	Roentgen rays, vaccines, diet, topical remedies	Roentgen rays, vaccines, ultraviolet rays, diet, topical remedies
General medical history	"Many indefinite conditions, nature of which could not be determined"	Many indefinite conditions, nature of which are indeterminable by extensive medical work-up
General condition	Essentially normal	Essentially normal
Psychiatric opinion	"Somewhat neurotic"	Decidedly neurotic
Laboratory observations	Blood cell count: r.b.c. 4,460,000, w.b.c. 5,600, normal differential count; normal urine; blood chemistry (mg./100 cc.): calcium 10.8, sugar 107.1, urea nitrogen 13.04, chlorides 495, cholesterol 250, phosphates not done; basal metabolic rate —19 per cent	Blood cell count: r.b.c. 4,410,000, w.b.c. 6,800, normal differential count; normal urine; blood chemistry (mg./100 cc.): calcium 11.8 (normal 9.6-11), sugar 85 (normal 80-120), urea nitrogen 14 (normal 10-15), chlorides 445 (normal 450-500), cholesterol 135 (normal 160-230), phosphates: specimen hemolyzed 3.5-4; basal metabolic rate —16 per cent (1941), —10 per cent (1947)
Size of recovered osteomas	0.5-2 mm.	0.5-1.5 mm.
No. of recovered osteomas	30-50	12
Roentgen observations of soft parts	Not made	Multiple minute soft tissue calcific deposits in the skin of the chin, around the nose and brow (Dr. Wm. H. Meyer)
Cell structure of specimen	Lamellated in concentric rings; numerous lacunae, most of which contained stainable nuclei; one or two haversian canals were seen containing small vessels; specimen in situ	Concentric arrangement of structure showed numerous lacunae containing stained nuclei which gave the impression of being those of osteoblasts; specimen not in situ; this appearance occurs whether or not the specimens are in situ (Dr. M. N. Richter)
Microchemical qualitative analysis	Calcium, phosphates, carbonates	Calcium, phosphates, carbonates, trace of protein, no silica

of the relevant and comparative data of both cases. Moreover, comparison of the photographs herein printed with those in Hopkins' article and with those of other cases shows further near-perfect similarity

between Hopkins' case and my own and the differences between these 2 cases and the others.

REPORT OF A CASE

G. S., a white woman aged 34, a stenographer, has been under continuous observation and treatment at the New York Skin and Cancer Unit and in the general medical and surgical services of the New York Post-Graduate Medical School and Hospital for the past seven years. Prior to that she was registered in the Stuyvesant Square Hospital Skin Clinic, in 1927, with the diagnosis of acne vulgaris. During the period of recent history her complaints had ranged through

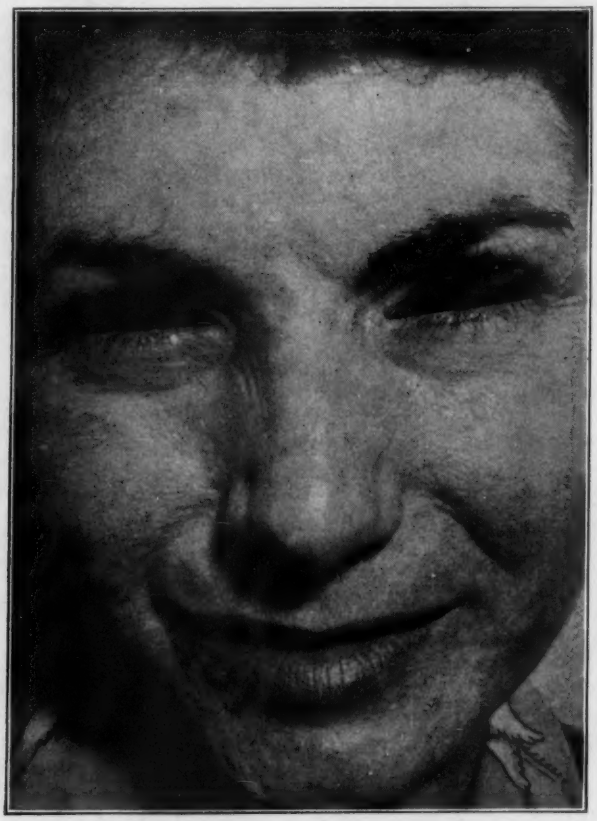

Fig. 1.—Clinical aspect of the patient.

many organs and systems, and if not yet quite all, then there is more to come. As a consequence, this patient's chart is thick with "work up." The results of these extensive clinical and laboratory examinations may be summed up with matching brevity: essentially normal except for the skin and the psyche. Literally, the dentist, proctologist, internist, surgeon, radiologist and clinical pathologist have not been able to reveal or establish any significant deviation from the normal. Only the dermatologist and the psychiatrist have found faults.

The dermatologic complaints involve the skin of the face. A history of acne goes back twenty-one years (to age 13). By the time I received the case, the chief

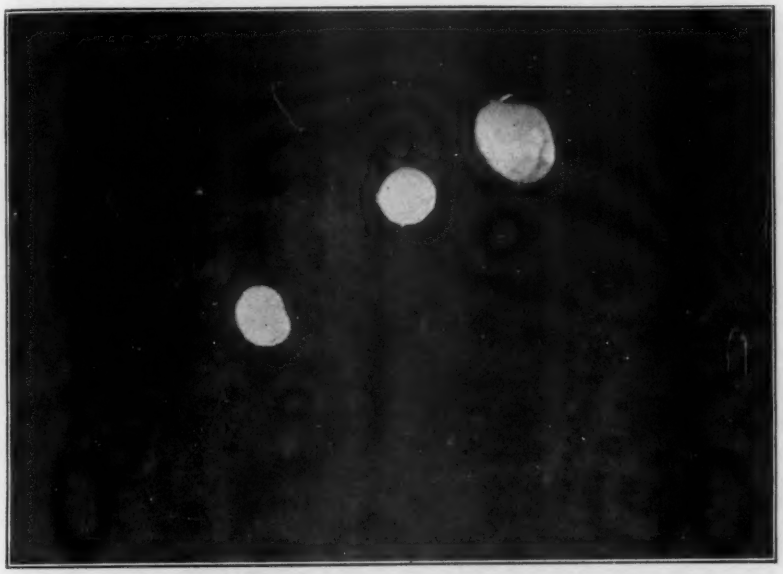

Fig. 2.—Gross appearance, showing size of osteomas (× 8.3) against a millimeter scale.

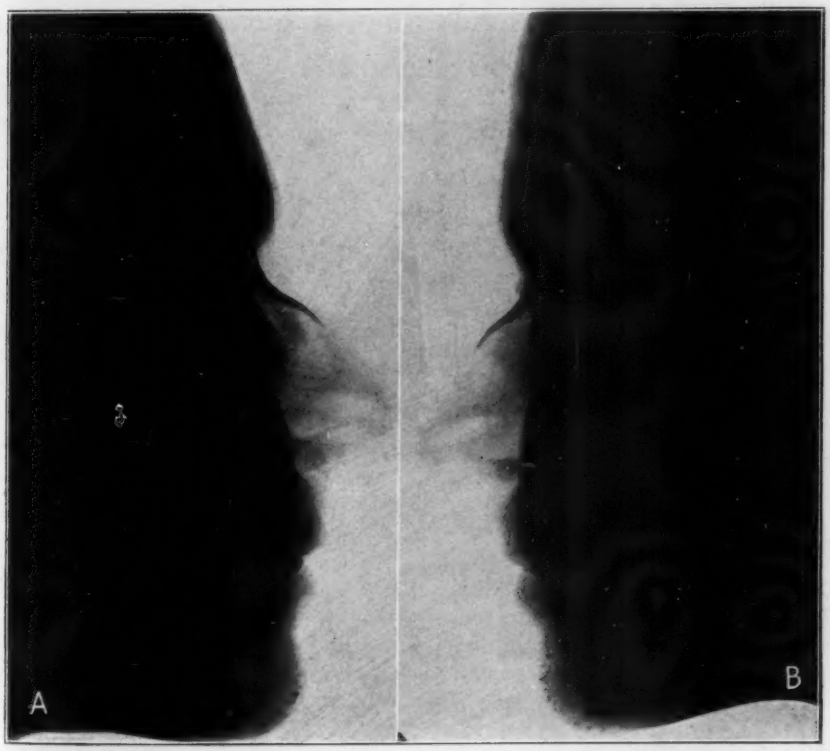

Fig. 3.—Contact reproduction of roentgenogram, soft parts technic. *A*, right side. *B*, left side.

complaint was no longer a simple statement like "I still get pimples on my face"; rather it was an involved and sophisticated account of previous studies and treatments, both orthodox and self prescribed. This patient's approach to the physician was more like that of a physician himself to a competent technician or at least as one technically equal colleague to another. The patient made requests for recondite investigation (e.g., allergy tests on this occasion) and engaged in a cooperative weighing of new diagnostic and treatment possibilities. New diagnoses and treatments were grasped at eagerly. Needless to say, by this time all standard therapy, i.e., radiation (roentgen rays), vaccines, ultraviolet radiation, dietetic restrictions,

Fig. 4.—Contact reproduction of roentgenogram of skin of cheek on dental film.

traditional topical remedies and routines, had been received. It also goes without saying that the results have not been very satisfactory.

Dermatologic examination at the start of this course of observation and treatment showed a picture (fig. 1) of some acne scarring, with very little frank acne activity, considerable traumatic scarring and neurotic excoriation (dermatitis factitia), rosacea-like erythema and telangiectasia. There were no milia. A diagnosis of acne excoriée des jeunes filles could apply. Cryotherapy and psychotherapy were suggested, planned and prescribed. The patient accepted gleefully.

It might have been easier, and I confess that the temptation was strong, to dismiss this patient as hopelessly maladjusted and therefore incurable, both derma-

tologically and psychologically. However, by evincing some sympathy I was soon rewarded by the presentation of something new in the form of several specimens of what looked exactly like grains of coarse sand (fig. 2). The patient claimed that she extracted them from the skin of her face. At first I thought that here was a

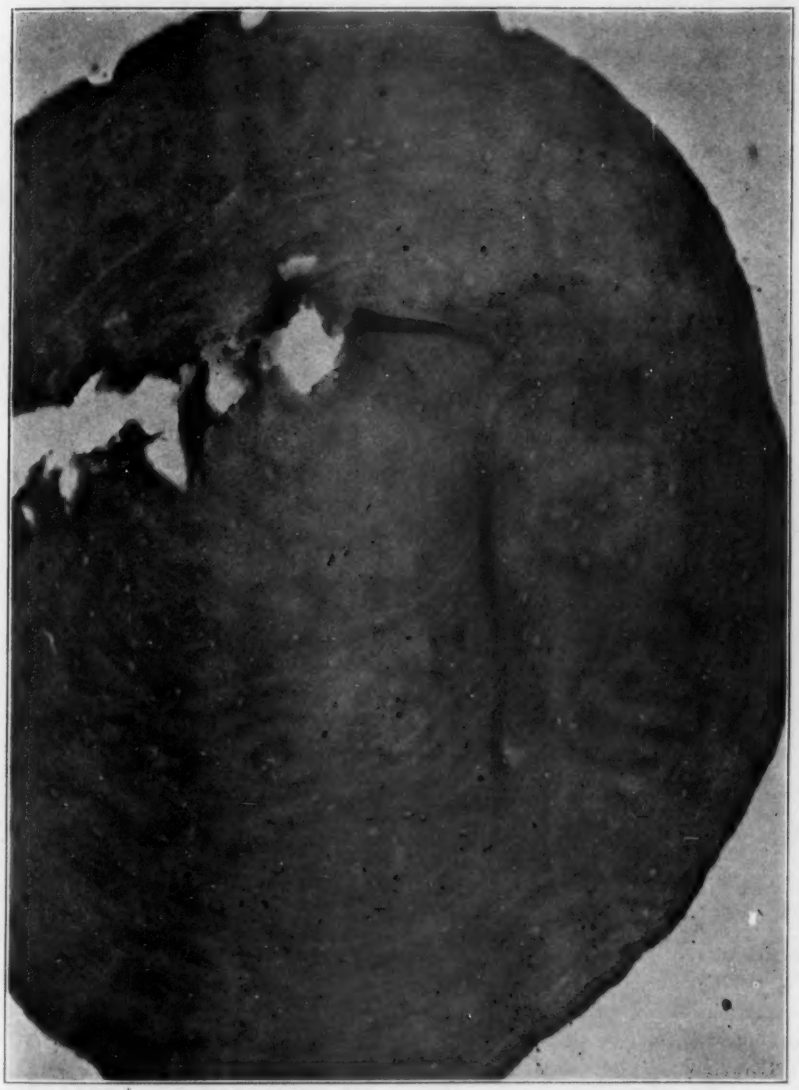

Fig. 5.—Photomicrograph of a sectioned osteoma (decalcified, stained by hematoxylin and eosin, × about 125).

new dermatosis to report, namely, an unheard of case of "silicosis cutis." To the patient I suggested that she was palming off actual sand grains, perhaps even honestly and unconsciously deluding herself by a most skilful legerdemain. The patient was not to be shaken, however, and blandly recalled that she had extracted

such a pellet for the first time when she was 18 or 19 years old, but not again until very recently. Up to this writing about twelve separate grains or tiny pebble-like concretions have been submitted by the patient. She did not claim to be able to locate the deposits in her skin or to know exactly where or when one may be present or found. However, by hit or miss digging—and the word digging is literally descriptive of her assault on the skin, a sort of quarrying operation—she finds one or two from time to time. At no time could the patient point out a sure spot for biopsy or extract one of these bodies under direct observation. Biopsy of what was vaguely thought to be a likely spot in the patient's judgment showed no

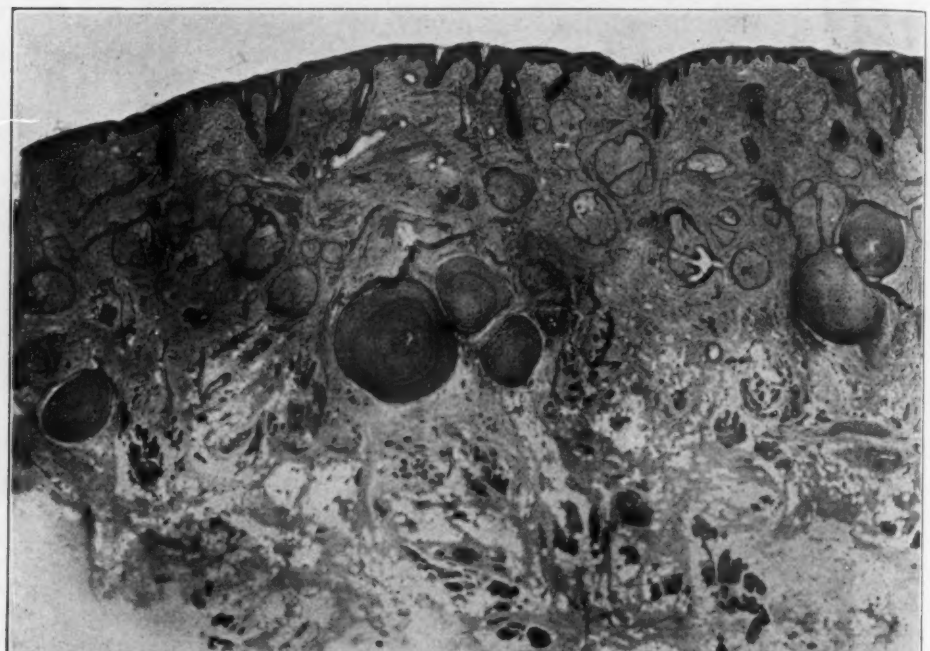

Fig. 6.—Photomicrograph of a section of skin from the chin showing six osteomas in situ (× 20.2).

bone on histologic processing. Examination of the skin under ordinary hand lens magnification and by palpation with most epicritical attention revealed no certain or reasonably likely places. However, roentgen examination of the skin of the face uncovered many tiny radiopaque (calcific) shadows in several places (figs. 3 and 4).[4]

The specimens submitted by the patient were subjected to microchemical qualitative analysis and to microscopic examination after decalcification and section. The resulting observations proved that they were indeed spherules of typical bone (the table includes a pathologist's[5] description and figure 5 shows the appearance

4. Dr. William H. Meyer made the roentgenologic studies.
5. Dr. M. N. Richter made the pathologic examination.

under the microscope). Finally, biopsy of the chin, with roentgenographic aid, showed six osteomas in situ in about 1 cm. (linear) of tissue (fig. 6).

COMMENT

Until the bony deposits in this case were demonstrated in the skin of the face by soft parts roentgen technic, some critics of this case, putting great stress on the psychopathic habitus of the patient, were not convinced that the specimens she submitted were not marvelously contrived artefacts. They even went so far as to call it "Bones (Bowen's) Disease." However, even without roentgenographic proof or proof by extraction under direct observation, it is inconceivable that anyone but an artisan of highest ingenuity could construct such pearl-like globules with the gross appearance and the orderly internal structure here seen—to say nothing of the impossibility of inserting the microscopically demonstrable osteoblasts. Despite the psychiatric vagaries of the subject involved and even without the conclusive objective observations, the case would be reasonably established.

Until the cell structure of the specimens was resolved as that of typical bone, other critics expressed the belief that the concretions, even if genuinely plucked from the skin of the face, could be cutaneous calculi rather than osteomas. Cutaneous calculi are said to occur in milia. Ormsby and Montgomery's textbook [6] contains a two sentence reference to such events as follows:

> In rare instances the deposition within milia of the salts of lime renders them as hard as cartilage (cutaneous calculi). These are usually of larger size [than ordinary milia, I suppose] and present a faint yellowish hue.

Ormsby and Montgomery do not go on to state what the microscopic structure of such calculi might be, but I imagine, judging from salivary, ureteral and vesical calculi, that they must be rather structureless or crystalline if milia are merely retention products of sebaceous glands; or if not amorphous, then laminated like a geologic specimen or vaguely preservative of the epithelial onionlike capsular appearance of milia that are concentric or horny cysts. In any event, this patient was devoid of milia clinically, and the microscopic picture of her concretions is indisputably more than these possibilities; i. e., it is that of true bone. Unless cutaneous calculi have been microscopically analyzed to be different from what has been herein conjectured above (and I know of no reference other than that in Ormsby and Montgomery), then Costello's case [2g] suggests that bony hard concretions in milia are osteomas and not calculi. It is possible, too, that Costello's case is not one of ossified milia despite the clinical resemblance, but rather multiple miliary osteomas of the face

6. Ormsby, O., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 1205.

like Hopkins' case and much like mine—with the exception that in my case the concretions were not clinically detectable by surface examination.

The pathogenesis of osteoma cutis is, of course, obscure. Speculation is all that can be offered but still may be worth while. First, it is well to recall that a distinction is made between metaplasia into bone and neoplasia of bone. Metaplastic ossification is fairly common and occurs readily enough secondary to calcification, chronic inflammatory processes and other preexisting irritative states. Neoplastic ossification is to be expected in malignant conditions of bone, but benign bony neoplasia (osteoma, osteosis) as it occurred in this case is undoubtedly rare. Theorization about embryonal rests of osteoplastic elements and nevus tardus development of such rests into true bone is inconclusive, but may be as near to the real situation as it is possible to come at the moment.

The only other suggestion that I can advance is that the condition in point is actually metaplasia after all, rather than neoplasia. The ossification may be conceived as being secondary to prolonged and persistent trauma in an area of skin that is exposed, that is well worked and hard working otherwise and that is rich in vascular structures and particularly rich in muscle elements. One may well imagine, remembering the ossifying myositis of equestrians and the relative ease with which bone forms in bruised striated muscle generally, that continuous pressing, squeezing and scratching of the skin of the face by patients like the one of this report may result in chronic inflammation of some of the tiny muscles of striated or smooth variety that are plentifully present in the facial skin to give it expressiveness. In the course of time, some of these loci of damage may become calcified and eventually ossified into minuscule masses of bone, as here found.

RINGED HAIR

Report of a Case

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AND
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RINGED hair, or, as it is also termed, pili annulati and leukotrichia annularis, is an abnormality which has interested physicians for a hundred years, and its cause is still unsolved. Karsch,[1] in 1846, was the first to describe this anomaly and called it "ringel haare."

Galloway [2] in 1896 reported two brothers with this rare disease and was the first to state that it was hereditary. Since then, Cady and Trotter,[3] Snell and Foley,[4] Reyn [5] and Juon [6] reported ringed hair in several generations. Snell and Foley and Juon have traced its incidence through four generations. Cady and Trotter in 1922 wrote an extensive treatise on this anomaly.

Our case is the first to be reported in the American literature since Snell and Foley's paper in 1932 and the first recorded case in which the axillary hair was also involved. Scalp hair is the common site involved, though ringed hair has been noted in the beard. In rare instances, teeth and nail changes have accompanied ringed hair. Up to the present, including our patient and her sister, 87 cases of ringed hair have been reported. This includes cases without microscopic examination, reported by authors as occurring in families.

From the New York Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Karsch, A. F. F.: De capillitii humani coloribus quaedam, Gryphiae, F. G. Kunicke, 1846, p. 39.

2. Galloway, J.: Case Report of Ringed Hair, Brit. J. Dermat. **8**:437 (Nov.) 1896.

3. Cady, L. D., and Trotter, M.: A Study of Ringed Hair, Arch. Dermat. & Syph. **6**:301 (Sept.) 1922.

4. Snell, G. D., and Foley, F.: Inheritance of Ringed Hair, J. Hered. **23**:155 (April) 1932.

5. Reyn, A.: Pili Annulati Occurring as a Family Disorder, Brit. J. Dermat. & Syph. **46**:168 (April) 1934.

6. von Juon, M.: Eine Beobachtung familiaren Auftretens von Pili anulati, Dermatologica **86**:117 (Aug.-Sept.) 1942.

Ringed hair is not due to pigment deficiency or pigment atrophy, as there is an equal amount of pigment throughout the hair. Speiss,[7] in 1859, first pointed out that ringed hair is due to the inclusion of gas bubbles in the medulla of the hair. The gas present in the medulla refracts the light, making that area appear white. Subsequent reports all verify this observation, but as yet no one has identified the true nature

Fig. 1.—Scalp showing alternate light and dark segments in the hair, especially in the area of the part.

of the gas or how it is formed. However, Cady and Trotter stated the belief that it is most likely carbon dioxide because the segmented appearance disappears when the hair is immersed in 5 per cent sodium hydroxide.

REPORT OF A CASE

G. A., a woman aged 26 years, had the condition of the scalp observed by us since birth. She was first seen on March 7, 1946, at the New York Skin and Cancer Unit. The patient's only illnesses were chickenpox and mumps in childhood. The patient's tonsillectomy at 2 years resulted in the regrowth of the tonsils. She came to the clinic because of a blue-brown dirty discoloration of the distal portion

7. Speiss, A., cited by Landois, L.: Des plotzliche Ergrauen der Haupthaare. Virchows Arch. f. path. Anat. **35**:575, 1866.

of the finger nails, which had been present for two years. A history was obtained revealing the use of a mercurial ointment on the nails. Discontinuance of the ointment resulted in normal nails.

A distinct dusty appearance of the patient's scalp hair was noticed. The hair appeared beaded. However, this appearance was caused by alternate light and dark segments in the hair. The condition was present throughout the scalp but was more prevalent in the posterior portion. The hair did not appear broken. The axillary hair appeared ringed macroscopically. The pubic hair was normal.

The father's scalp hair was normal. The sister's scalp showed typical ringed hair both macroscopically and microscopically. There was no history of similar appearing hair in any other member of the family.

Examination of the patient's scalp under filtered ultraviolet rays showed no unusual fluorescence. However, close inspection of a single hair under filtered ultraviolet rays revealed that the light areas fluoresced a dull white.

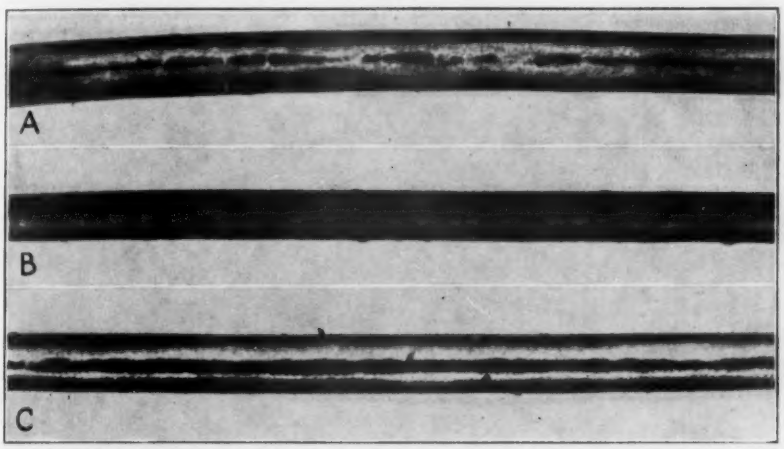

Fig. 2.—*A*, photograph of an axillary hair taken by transmitted light, showing typical dark segments in the medulla. Similar appearance in the hair of the scalp. *B*, photograph of normal brown hair taken by transmitted light. *C*, normal gray hair showing uninterrupted dark medulla, which was due to gas bubbles.

Microscopically, both the scalp hair and axillary hair presented uniform diameters, with no beading present. There was no atrophy or fragmentation of the hair. Throughout the entire length of both scalp and axillary hair were alternate light and dark areas in the medulla.

The light areas observed macroscopically (reflected light) were caused by the presence of gas bubbles in the medulla of the hair. Microscopic examination with reflected light revealed the gas bubbles to be present in the light areas. However, examination by transmitted light showed the areas in reverse, the former light areas appearing dark and the former dark areas appearing light.

SUMMARY

A case of ringed hair involving both scalp and axillary hair is reported. A sister also had ringed hair in the scalp.

57 W. Fifty-Seventh Street.
52 Broad Street.

FAVUS IN A RURAL COMMUNITY OF NEW YORK

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NEW YORK

THREE cases of favus of the scalp were observed recently in Greenport, Long Island, 96 miles from the city of New York, with a population of approximately four thousand, five hundred. The community consists of a mixed population of both native and foreign born. The 3 cases of favus which were discovered there were all verified by mycologic examination. Cultures of the scales and hairs showed a growth of the causative organism, Achorion schoenleinii, and on microscopic examination, the individual hairs from each patient yielded typical large spores in chains, with air bubbles attached. Favic chandeliers and chlamydospores were observed in the culture mounts in all 3 cases.[1]

During the past twenty-five years there have been scattered reports of the sporadic incidence of the disease in many states.[2] However, favus has been seen much more frequently in Austria, England, France, Scotland, Russia and Poland. Bergeron [3] stated that it is a disease of rural districts and that most patients with favus seen in large cities come from the country.

Aside from the comparative rarity of the disease, one of the interesting features of the minor epidemic which is here reported was the discovery of the carrier.

From the New York Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University (now New York University-Bellevue Medical Center).

1. Mrs. A. Casper, B.S., of the Skin and Cancer Unit, conducted the mycologic examination.

2. Dey, N. C.: Notes on Common Skin Diseases: Ringworm of the Scalp; Favus, Indian M. Gaz. **76**:416-417 (July) 1941. Reque, P. G.; Barefoot, S. W., and Conant, N. F.: Tinea Favosa of the Scalp, North Carolina M. J. **2**:329-343 (July) 1941. Muskatblit, E.: Tinea Favosa: Report of Six Cases, M. Rec. **151**:187-191 (March 20) 1940. Epstein, N. N., and Levin, E. A.: Favus Infection: Report of a Case from California, Urol. & Cutan. Rev. **42**:515-517 (July) 1938. Lewis, G. M.; Rosenfeld, H., and Hopper, M. E.: Favus of the Glabrous Skin, M. Rec. **145**:189-191 (March 3) 1937. Kerr, P. S.: Case Report: Favus in Native School Child, New York State J. Med. **35**:781 (Aug. 1) 1935. Tobias, N.: Favus of the Scalp: Report of Cases, J. Missouri M. A. **26**:212-214 (May) 1929. Barrett, C. C.: Incidence of Favus in Kentucky, Arch. Dermat. & Syph. **33**:126-127 (Jan.) 1936. Rutledge, W. W.: Report of Case of Favus, Kentucky M. J. **34**:149-151 (April) 1936. Morris, G. E.: Favus in Massachusetts, New England J. Med. **230**:667-669 (June 1) 1944.

3. Bergeron, cited by Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Philadelphia, Lea & Febiger, 1943.

REPORT OF CASES

CASE 1.—In June 1945, Miss D. T., age 15 years, was seen by me in consultation with Dr. J. Mott Heath, Suffolk County Health Officer, and Dr. William W. Kaplan of Greenport, Long Island. She was a white girl, born in the United States, whose general health was good. She presented the typical clinical picture of favus with thick scales, scutula and areas of partial alopecia diffusely scattered over the scalp (fig. 1). No significant abnormalities were revealed in general examination of the glabrous skin, appendages and nails. The duration of the disease was three years. A. schoenleinii was evident in microscopic examination of the hairs and in cultures. Examination of the scalp with filtered ultraviolet rays demonstrated a yellowish green dull fluorescence of scales and hairs. There were interspersed areas of atrophic alopecia. The patient was one of seven children. No other member of the family had favus.

The father of the patient volunteered the information that several other children in the village were known to have "ringworm of the scalp." He also stated that

Fig. 1 (case 1).—*A*, before roentgen epilation, showing areas of atrophy, scaling, scutula and diseased hairs. *B*, view of scutula, diseased hairs and atrophic alopecia during defluvium after roentgen epilation.

his married daughter was now living in a house which had been previously occupied by a family whose members were known to have "ringworm." With this as a possible clue to the source of the favus infection, the county medical officer of the locality, Dr. Heath, arranged to have all the members of the suspected family examined by me. The following 2 cases are of members of that family who were examined and proved to have the disease.

CASE 2.—M. N., a white boy aged 7, born in the same village, had, according to the mother, discolored hair since early infancy, although there had been no areas of baldness. Gross examination revealed patches of a greyish green discoloration scattered over the scalp (fig. 2). There were no scales, although there was a mousy odor. There was no alopecia or atrophy. General examination of the glabrous skin disclosed no significant abnormalities. A yellowish green dull fluorescence was observed under filtered ultraviolet radiation. Favus was demonstrated in microscopic and cultural examination of the hair. Questioning of the

mother revealed that the father of the child had been suffering from a disease of the scalp since the age of 9. Thereupon an examination of the father was requested (case 3).

CASE 3.—M. N., a white man aged 33, was the father of the aforementioned child (case 2). He was born in the United States, of Lithuanian parentage. Examination revealed a dollar-sized area of atrophy on the vertex of the scalp, with several hairs growing normally in the center. The remainder of the scalp was clinically normal. There was no fluorescence demonstrated with filtered ultraviolet radiation. Favus was demonstrated both microscopically and culturally on several hairs removed from the periphery of the atrophic area. The patient reluctantly admitted that the disease had been present since early childhood. About fifteen years previously he had consulted a local physician who had treated the area with roentgen rays, and the scales disappeared. A sister of the patient was examined and proved to be free of the disease.

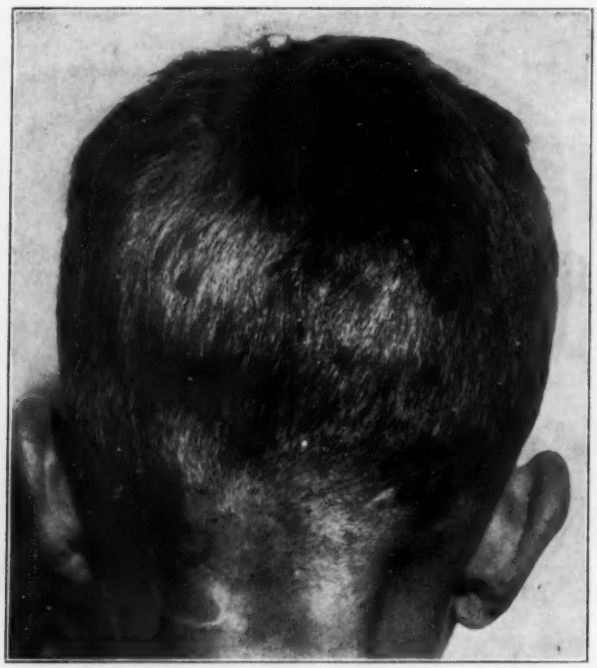

Fig. 2 (case 2).—Discoloration of hairs without scaling or scutula.

COMMENT AND SUMMARY

Three cases of favus of the scalp are reported from a rural community with a population of four thousand five hundred, lying approximately 96 miles from the city of New York. All 3 patients were native born. The disease produced different clinical manifestations in each case, and microscopic observations were all similar. Although in the oldest

patient (case 3, the father) some local immunity to favus had evidently developed over a period of fifteen years and the disease had been localized to but one circumscribed area on the scalp, it was proved that he was the carrier, as evidenced by the presence of favus in his child (case 2). The fact that members of the two families shared the same house at different periods leads one to infer that the disease might have been transferred by an animal or parasite or that infected human hairs remained in the house.

It has been suggested that further investigation be made of cats, rats, mice and other possible carriers in the community. A more complete and careful examination of the local inhabitants has also been advised.

30 East Sixtieth Street.

ERYTHROPLASIA OF QUEYRAT

Report of Ten Cases

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AND
PERRY M. SACHS, M.D.
NEW YORK

ERYTHROPLASIA is a rare disease and was first described in 1893 by Fournier and Darier.[1] Since Queyrat's [2] studies in 1911, the disease has been known as erythroplasia of Queyrat. Sulzberger and Satenstein,[3] in 1933, reported the first case in the American literature. Approximately 50 additional cases have since been presented at various dermatologic societies in this country, in addition to reports by Stiles [4] and by Irgang and Alexander.[5]

In spite of the rarity of cases, there has been considerable discussion concerning this disease. It is our purpose in this paper to report our observations in 10 cases. We intend to show that in these instances there was no clinical or microscopic evidence of malignancy or premalignancy and that lesions develop not only on mucous membranes but also on glabrous skin. Suggestions as to therapy also are offered.

The 10 patients reported here presented typical clinical pictures and previously had been given a diagnosis of and treatment for erythroplasia by many competent dermatologists. The diagnosis was corroborated in 9 cases by microscopic examination. However, in 1 case no biopsy was performed. Several of the patients were presented before different dermatologic societies.

We have omitted detailed descriptions of cases, as they prove repetitious and furnish little additional information to the following salient and pertinent features noted in our series. All the patients were Jewish men, 25 to 50 years of age, who had lesions on the glans penis.

From the Department of Medicine (Dermatology), New York Hospital and Cornell University Medical College.

1. Fournier, A., and Darier, J.: Epithéliome bénin syphiloide de la verge (epithéliome papillaire), Bull. Soc. franç. de dermat. et syph. **4**:324-328, 1893.

2. Queyrat, L.: Érythroplasie du gland, Bull. Soc. franç de dermat. et syph. **22**:378-382, 1911.

3. Sulzberger, M. B., and Satenstein, D. L.: Erythroplasia of Queyrat, Arch. Dermat. & Syph. **28**:798-806 (Dec.) 1933.

4. Stiles, F., Jr.: Erythroplasia of the Glans Penis (Queyrat), Arch. Dermat. & Syph. **30**:647-650 (Nov.) 1934.

5. Irgang, S., and Alexander, E. R.: Erythroplasia of Queyrat in a Negro: Report of a Case, Arch. Dermat. & Syph. **34**:247-250 (Aug.) 1936.

However, 3 patients also showed involvement of the scrotum (fig. 1), 2 manifested patches on the shaft of the penis (fig. 2) and 1 had a lesion on the lower part of the abdomen. Early lesions began as small erythrematous macules or slightly elevated papules, about 0.5 cm. in diameter. They extended peripherally, frequently covering the entire glans penis. The lesions appearing on the glabrous skin developed slowly and did not become large. Papules or patches of erythroplasia are red, shiny or velvety, not indurated and usually moist. There was no

Fig. 1.—Erythroplasia involving the scrotum.

scaling, but often crusting. Subjective symptoms varied from complete absence of discomfort to severe stinging or itching. When the meatus was affected patients complained of burning on urination. The Wassermann and Kahn serologic reactions were negative. Two patients, in the history of their past illness, described generalized eruptions that indicated the possibility, in both instances, of exudative discoid and lichenoid chronic dermatosis. However, it is not our intention to imply any relation between the two diseases.

While in our series all were white men, the disease has been described in women and in Negroes. Erythroplasia has been reported in circum-

Fig. 2.—Erythroplasia of the shaft of the penis as well as the glans.

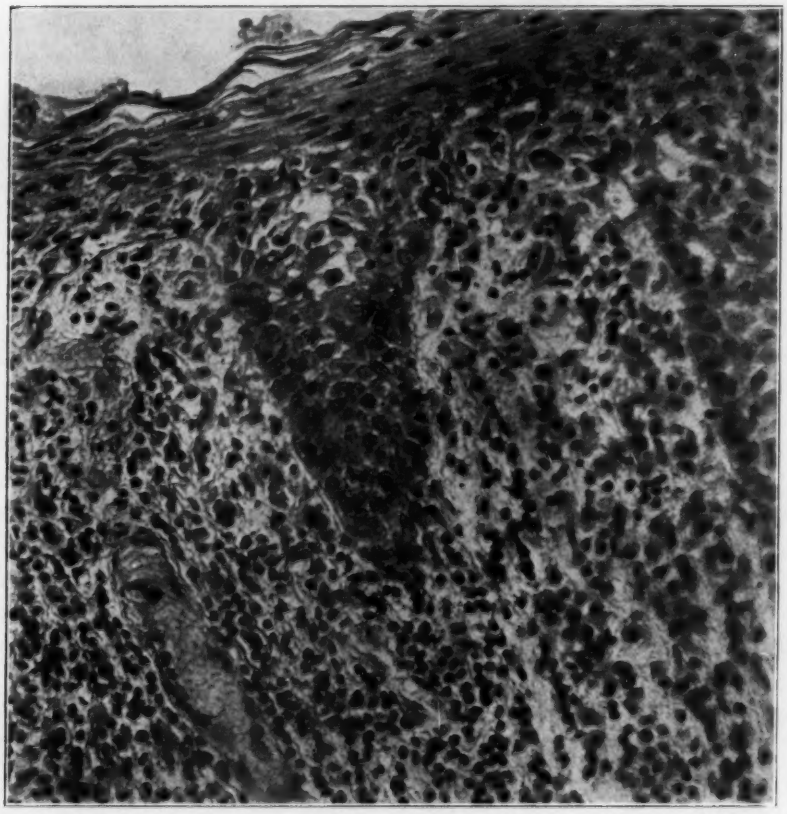

Fig. 3.—Erythroplasia showing peg-shaped rete pegs, surface of the epidermis and the cellular infiltration (× 226).

cised and in uncircumcised men. Additional sites for erythroplasia are the prepuce, oral mucosa, lips and vulva. Our microscopic studies were not limited to the cases reported here, but included several others of the same type, as well as 1 case of a lesion of the buccal mucosa and 1 of a lesion of the vulva. We have noted three histologic features that characterize erythroplasia: the shape of the rete pegs, the surface of the epidermis and the type of cellular reaction (fig. 3). The epidermis

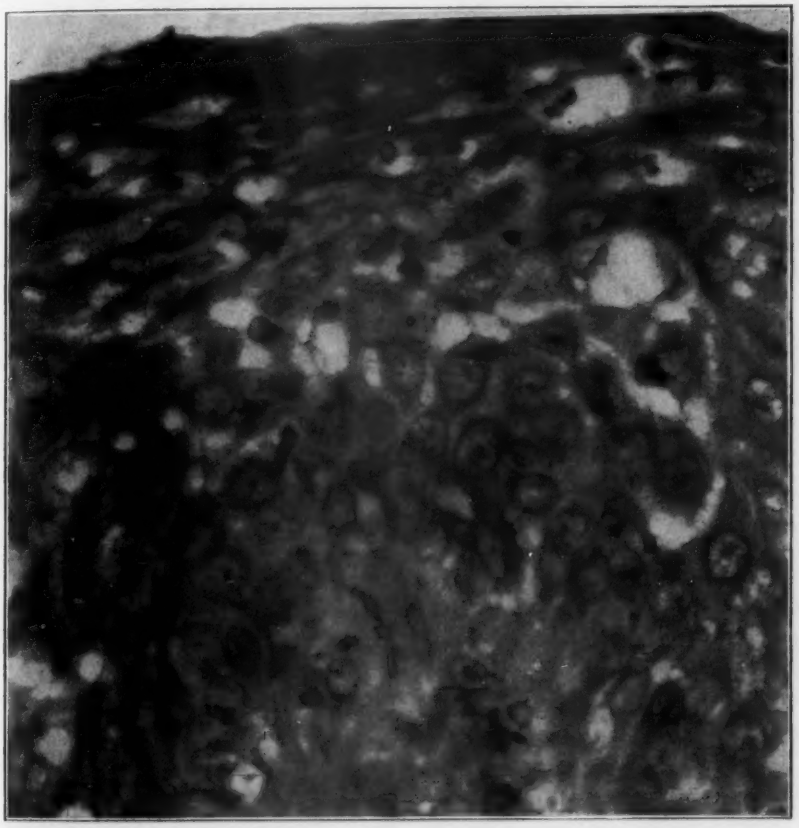

Fig. 4.—Erythroplasia showing the hydropic cells and the network-like appearance of the upper part of the epidermis (× 673).

is irregularly and moderately acanthotic, with triangular or distinctly peg-shaped rete pegs. The surface consists of a loose network arrangement of the superficial epidermic cells. These cells are hydropic and swollen, the cytoplasm is clear, the nuclei lie free within the cell and appear normal and mitotic figures are not evident (fig. 4). When the crust covers the surface the network-like architecture and the hydropic appearance of the cells are much less prominent. Intercellular edema may be noted in the lower portion of the epidermis (fig. 5).

The inflammatory reaction is in the upper and middle layers of the cutis, but it is most pronounced in the subepidermic region. The vessels are dilated, and a moderate interstitial edema is demonstrable. The cellular infiltration is perivascular, diffuse and usually moderately intense and consists predominantly of plasma cells. Small round cells and eosinophils may be present. Some of the cells may infiltrate into the epidermis.

Fig. 5.—Erythroplasia showing the crust formation on the surface of the epidermis (× 770).

COMMENT

The patients with erythroplasia reveal no serologic, clinical or microscopic evidence of syphilis. Cellular infiltration composed mainly of plasma cells, which is seen in erythroplasia, may be present not only in syphilis but in many other dermatoses. Also, the vascular changes characteristic of syphilis are absent in erythroplasia. We believe that erythroplasia is not related to syphilis.

The dermatosis has been considered precancerous by almost all recognized dermatologic authorities. The French literature has fostered this view and has reported epitheliomatous development in practically all patients who could be followed for a sufficient number of years. A study of the cases recorded in this country revealed no definitely proved malignancy following erythroplasia. Moreover, 3 of our patients are cured, after the lesion had been present from three to five years. In 1 patient, the lesion persisted for fourteen years without any sign of carcinoma.

In our cases the microscopic picture showed no evidence of malignancy. Anaplasia, formation of whorls and pearls, keratinization, mitotic figures and dyskeratosis were absent. The hydropic state of the cells at the surface of the epidermis should not be construed as dyskeratosis. The reaction in the cutis is not that of an inflammatory protective zone, since it is diffuse and not limited to any particular region of the overlying epidermis. It is not different from any other inflammatory reaction, except that the cellular infiltration is composed chiefly of plasma cells.

Thus, the study of the few cases presented by us and those recorded in the American literature as yet lends no support to the concept that erythroplasia is an obligatory precancerosis or cancerosis. In fact, we are inclined to question this concept and believe that erythroplasia may be a productive inflammatory process and possibly a response to a specific agent.

TREATMENT

Perhaps this report is somewhat premature. We had hoped to outline a definite and distinct cure for the disease, but at present we cannot do so. Considering the presumed seriousness of this disease and since we have cured 3 and probably 4 patients, we have decided to submit the description of the therapy as far as we have progressed as a preliminary report. It should be stressed that occurrences of the disease are infrequent and that all except 1 of our patients previously had been treated for at least one and a half to fourteen years by competent dermatologists.

We entertained the thought that erythroplasia might be caused by an organism involving the vaginal tract, such as Trichomonas or a spirochete other than Treponema pallidum. We considered the possibility of a relationship to Vincent's infection. This concept was based on the location, behavior and some of the microscopic features of the disease. Since various factors prevented investigation we cannot attest to the validity of this concept.

Treatment with preparations with arsenic has been successful in Trichomonas vaginalis, Vincent's infection and spirochetal diseases. This led to the belief that the same therapy might be succesful in erythroplasia. We have used neoarsphenamine intravenously, and neoarsphenamine, tryparsamide, oxophenarsine hydrochloride and acetarsone

(cinquarsen®) locally, all with beneficial results. (Treatment with bismuth compound proved of little value.) However, the best therapeutic effect was obtained with neoarsphenamine, 0.3 Gm. dissolved in 4 cc. of distilled water to which 1 cc. of glycerin was added. When arsenic compound was used in powder form or in glycerin alone the improvement was not pronounced.

The aqueous solution of neoarsphenamine is swabbed on the lesion lightly twice a week for about two or three weeks. Then it should be applied only when indicated by continued oozing. The solution as described often may prove too strong and in these circumstances should be diluted three or four times. It is important to remember that the arsenic compound should not be employed in too concentrated a form or for too long a period, because of excessive crusting that follows.

After application of the solution the lesions become dry and form heavy crusts, which progressively develop into warty excrescences. We have been unable to remove this crust without causing exacerbation. In our attempts to separate the crust, we have tried boric acid wet dressings, boric acid ointment, solution of calcium hydroxide, isotonic solution of sodium chloride, cold cream, an oxycholesterol-petrolatum ointment base (aquaphor®), saliva, milk and other agents, but without success. However, the crust disappears in time (up to two years), leaving no trace of the disease.

The patients experienced no pain or discomfort. The exudation and subjective symptoms disappeared within a few weeks and sometimes in a few days. The solution seems to have no influence on the normal skin or the uninvolved portion of the glans penis. We have seen no unfavorable reaction to this medication.

A résumé of the progress of the 10 patients shows that 3 are cured, 1 for over five years, another for three years and the last for one year. We were unable to follow completely 2 patients, but we have reason to believe that 1 is practically if not entirely well. Our first patient was treated in the conventional manner, because we were then unaware of the treatment herein suggested. This patient has remained well for twelve years after superficial cautery of a lesion extending over most of the glans penis. The remaining 4 patients are still under treatment. Two are almost well, while the other 2 have been seen for only a short time.

SUMMARY AND CONCLUSIONS

A new and nondestructive treatment for this disease with some apparent cures is outlined.

Lesions of erythroplasia may develop not only on the glans but also on the shaft of the penis, the scrotum and the lower part of the abdomen. We, like previous observers, believe that erythroplasia is unrelated to syphilis. In contrast to other observers, we question the concept that erythroplasia is precancerous or cancerous.

PARA-AMINOBENZOIC ACID AND INDOLE METABOLISM

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FOR THE past few years I have in private practice prescribed para-aminobenzoic acid in a variety of dermatoses, including hair and scalp conditions. A surprisingly common subjective response to this therapy has been a feeling of greater vigor, a loss of tired or enervated states. Some patients were so impressed with this result that they sought guidance in the use of the drug on other members of the family. My interest [1] in indole metabolism suggested a possible explanation of this subjective response on the basis of a reduction of protein putrefaction in the intestines with a consequent diminution in indole production.

Indole is a toxic substance, exclusively produced in the intestines by way of the bacterial degradation of the amino acid tryptophane. On absorption, approximately 50 per cent of it can be demonstrated as having been detoxicated by way of a conversion to the harmless indoxyl potassium sulfate (indican). The appreciable fraction of indole still unaccounted for after absorption represents the threat to the organism. Autointoxication is a word that has almost completely lost caste with clinicians (as has the adjective "bilious"), more because it lacks specificity in terms of cause as well as effect than because it is incompatible with concepts of pathogenesis.

Indole when ingested (5 mg.) produces loginess, headache, malaise and fatigue. Indole intoxication must in my opinion be a clinical reality which clinicians disdain to search for in spite of the many indictments still pending against indole, including the one of carcinogenicity. With indican excretion in the urine as a gage of the indole production, the use of quantitive methods for the measurement of this elimination has clinically established several facts with respect to indole formation in the intestines. Chronic obstipation increases its production, as do diets high in animal proteins. Vegetable diets lead to low excretions of indican.

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From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology of the New York Post-Graduate Medical School and Hospital (Dr. Marion B. Sulzberger, Director).

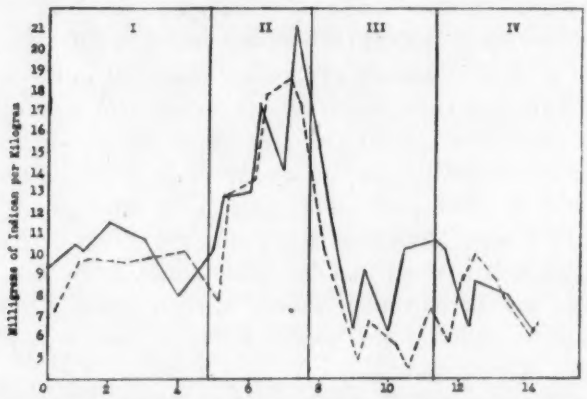
1. Sharlit, H.: A Method for the Quantitative Estimation of Indoxyl Compounds in Blood, J. Biol. Chem. **104**:115 (Jan.) 1934; The Concentration of Indoxyl Compounds (Indican) in Blood, J. Lab. & Clin. Med. **20**:850 (May) 1935; Indican Excretion in the New-Born, Arch. Pediat. **55**:277 (May) 1938.

Catharis causes a sharp fall in indican excretion for several days following its use.

Para-aminobenzoic acid, accepted as a member of the vitamin B group, has been allegedly capable of affecting changes in the intestinal bacterial flora. The experiment conceived and herein reported sought evidence of a twofold nature: (1) Can para-aminobenzoic acid influence the amount of indole production from a given standard diet, and (2) can para-aminobenzoic acid influence the degree of indole detoxication by its conversion to indican? While this conjugation of indole to indican involves hepatic function, no evidence exists demonstrating this functional capacity as exclusively hepatic.

EXPERIMENT

Two groups (A and B) of rats were used. All urine was collected, in which samples the total quantity of indican[2] was determined. These amounts were recorded



Graph summarizing data in the experiment described. The unbroken line relates to group A (control rats) and the broken line relates to group B (rats fed para-aminobenzoic acid). The horizontal row of figures at the bottom represents time in weeks. In period I, a basic diet of ground fox chow was fed both groups. In period II, group A was fed an average of 1.80 mg. of indole per rat plus the basic diet; group B received the same diet plus 15 mg. of para-aminobenzoic acid per rat. In period III, both groups were given the basic diet. In period IV, group A was fed the basic diet and group B received fox chow plus 15 mg. of para-aminobenzoic acid per rat.

as milligrams per kilogram of the average weight of the group. The time of the experiment was a continuous one, but divided into four parts.

For group A (control), part I was the control period to determine the amount of indican excreted on the standard diet; part II was the period in which indole was added to the standard diet; part III was the period in which the added indole had been removed from the diet and revealed the rate and time taken for the indican excretion to return to the base line, and part IV was a continuation of the study to

2. Sharlit, H.: A Method for the Quantitative Estimation of Indoxyl Compounds in Urine. J. Biol. Chem. **99**:537 (Jan.) 1933.

prove the stability of the base line reached in period III and to act further as control against period IV in group B.

For group B (experimental), the same procedure was used as for group A except for the addition to the diet in periods II and IV of adequate amounts of para-aminobenzoic acid ("paba").

COMMENT

These facts, as well as the amount of indole and para-aminobenzoic acid exhibited, are revealed in the accompanying graph.

The excretion curves for both groups were practically identical. One inference alone is permissible: Under the conditions of the experiment the exhibition of para-aminobenzoic acid influenced neither the production of the endogenous indole formed from the food protein nor the conversion of that or added indole to harmless indican by whatever organ (liver) or organs were involved.

This report is offered as representative of many pieces of work dealing with general medical problems being carried out in our dermatologic institution at the New York Post-Graduate Medical School and Hospital. It has been and continues to be our principle that dermatologists are both equipped and obligated to study general medical problems related to their field, and the problems of the metabolism of para-aminobenzoic acid, a substance used by skin specialists as a sun screen, as an anti-gray-hair factor and in other ways, properly comes within that category. In consonance with the principle just mentioned, Dr. MacKee has these many years made funds available to me for investigations dealing with fundamental metabolic and biochemical studies.

HEMANGIOPERICYTOMA

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STOUT and Murray,[1] in 1942, described a type of vascular tumor characterized by the formation of endothelial tubes and sprouts surrounded by closely packed, rounded and at times elongated cells. They demonstrated by tissue culture that these cells are derived from the capillary pericytes of Zimmerman [2] and suggested hemangiopericytoma as a properly descriptive name.

Various types of cells are closely applied to the outer surfaces of the capillaries, which in turn are composed of a single layer of endothelial cells. The pericapillary cells consist of connective tissue fibroblasts, histiocytes, mast cells, plasma cells, undifferentiated mesenchymal cells and in some instances an additional type of cell which has been called the Rouget cell and which, more recently, has been designated the pericyte. This contractile cell is spider-like, having numerous slender processes of a dendritic nature which encircle the capillary and serve to change the caliber of the lumen [2] (fig. 1). Using a silver chrome impregnation Zimmerman showed similar cells, which he called pericytes, encircling the capillaries of the human heart. He wrote that these cells were contractile and that they were modified smooth muscle cells. In man, pericytes have been demonstrated in the kidney, liver, heart, lung, intestine, pia mater and omentum.[3]

The adventitial cells of blood vessels are not pericytes, but are fixed stellate connective tissue cells.

Dr. Stout and Dr. Murray assisted in this work.

From the New York Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Stout, A. P., and Murray, M. R.: Hemangiopericytoma, Ann. Surg. **116**:26 (July) 1942.

2. Zimmermann, K. W.: Der feinere Bau der Blutcapillaren, Ztschr. f. Anat. u. Entwcklngsgesch. **68**:29, 1923.

3. (*a*) Zimmermann.[2] (*b*) Stout, A. P., and Cassel, C.: Hemangiopericytoma of the Omentum, Surgery **13**:578 (April) 1943.

Murray and Stout [4] have shown by tissue culture that the epithelioid cells of the glomus tumor are derived from Zimmermann's pericyte, and this led them to the investigation of other vascular tumors with cells arranged peripherally about the vessel walls. They [1] have reported 8 cases of hemangiopericytoma of the skin, 1 of the deep tissues of the thigh and 1 case of hemangiopericytoma of the omentum.[3b]

Fig. 1 (redrawn from Zimmermann).—Capillary and precapillary pericytes in the heart of a 43 year old man. *E*, endothelial cell; *P*, pericyte.

Four of these tumors were composed of endothelial tubes and sprouts, surrounded by pericytes. All four were excised without known recurrence. These tumors had, in addition to the rounded pericytes, certain areas in which the cells were spindle shaped and resembled smooth

4. Murray, M. R., and Stout, A. P.: The Glomus Tumor: Investigation of Its Distribution and Behavior, and the Identity of Its "Epithelioid" Cell, Am. J. Path. **18**:183 (March) 1942.

muscle cells. In some of their blood vessel tumors there was a probable relationship between pericytes and smooth muscle cells, because the cells arranged about the tumor vessels ranged from the usual round pericyte through an intermediate form of spindle-shaped cells to a fully differentated cell with myofibrils. In their [1] cases 5, 6 and 7 the observations in the histologic examination suggested strongly that the pericyte is related to the smooth muscle cell. The next step in differentiation would be represented by a tumor with no round pericytes, but composed mainly of fully differentiated smooth muscle cells. Tumors of this sort do exist and have been studied and discussed by Stout as cutaneous leiomyomas.[5] At that time the close relationship between those leiomyomas and their more recent group of hemangiopericytomas was not appreciated.

Stout and Murray stated in their report on hemangiopericytoma [1] that some of the tumors were excised without known recurrence. Their eighth case exhibited infiltrative growth. Ten operations had been performed within eleven years in attempting to remove a small tumor on an index finger, and the eleventh operation consisted of amputation of the finger with removal of three fourths of the metacarpal bone. Pericytes were the most conspicuous feature of the tumor and were arranged in lobules surrounding the vessels and endothelial sprouts. Their ninth patient had a tumor of the thigh which had been present three years and which measured 14 by 7 by 6 cm. when excised. There was no local recurence, but four years later there were observed in the liver five nodules, on one of which a biopsy was performed. The liver was treated with small doses of roentgen rays. The patient, whose health grew progressively poorer, died seven years after the first operation. The primary tumor and the metastatic node from the liver were composed of many endothelial tubes surrounded by closely packed rounded cells.

Pericytes are one type of cell in the perithelium; there are several others, and the perithelial origin of other types of tumors has been investigated. Becker and Thatcher,[6] in 1938, showed by tissue culture that Kaposi's sarcoma is a multicentric neoplasm apparently originating from embryonic mesenchymal cells (lymphoid cells of Marchand). These cells arise in the perithelial tissue and are but one of several types of cells making up the perithelium. In the development of the human embryo not all mesenchymal cells form mature cells; some remain undifferentiated and arrange themselves along blood vessels. In tissue culture and in inflammation they undergo progressive develop-

5. Stout, A. P.: Solitary Cutaneous and Subcutaneous Leiomyoma, Am. J. Cancer **29**:435 (March) 1937.

6. Becker, S. W., and Thatcher, H. W.: Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi, J. Invest. Dermat. **1**:379 (Oct.) 1938.

ment and furnish new cell types. These cells probably include the so-called pericyte (contractile cell of Rouget) and the undifferentiated cells of Marchand and those of Maximow.[7] Many different types of tissue cells are arranged along the capillaries—fibroblasts, histiocytes, undifferentiated mesenchymal cells, mast cells, plasma cells and pericytes. All these are considered as perithelium.

The hemangiopericytoma is a vascular tumor without sufficiently characteristic gross features to enable it to be recognized clinically, and

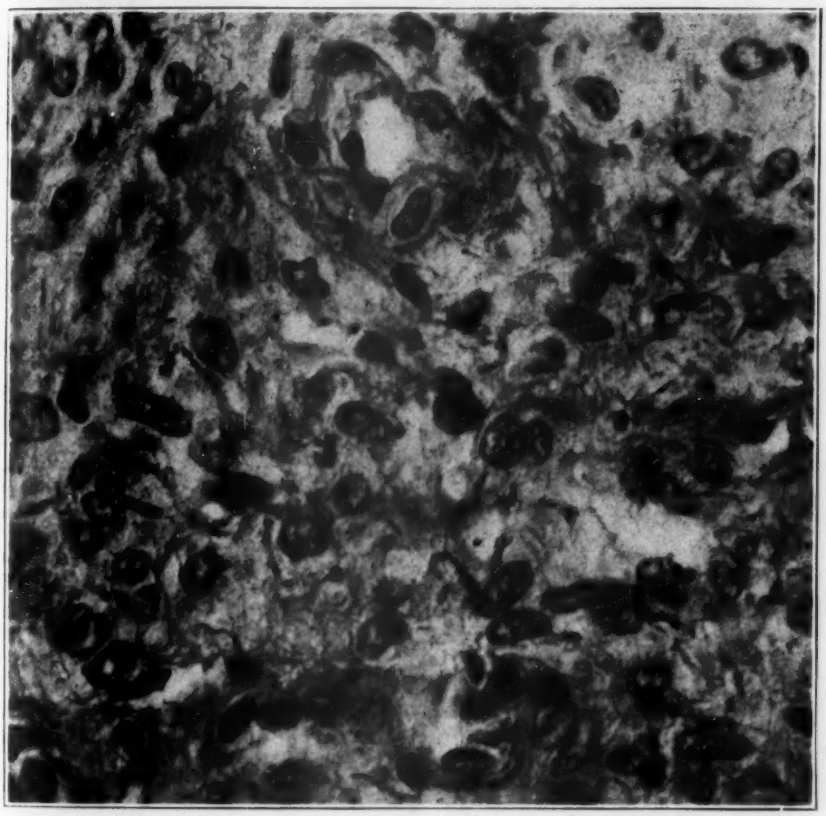

Fig. 2 (case 1).—Masses of pericytes surrounding vessels. × 775.

the diagnosis must be made by histologic examination. Clinically it may resemble granuloma pyogenicum, hemangioma, lymphangioma, angiosarcoma, glomus tumor or hemangioendothelioma.

REPORT OF CASES

CASE 1.—(Dr. A. P. Stout has permitted reporting of this case.) A tumor of the mons veneris had been growing in the subcutaneous tissue of a 43 year old

7. Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 3, Philadelphia, W. B. Saunders Company, 1938, p. 232, fig. 201.

woman for at least seven years. When excised, it was kidney shaped and measured 7 by 5 by 3 cm., and the tissue surrounding it was exceedingly vascular. It was a soft solid pinkish growth, mottled with red. There has been no recurrence in two years.

Figures 2 and 3 show that throughout the corium there were numerous dilated blood vessels of varying caliber. These vessels were surrounded by an enveloping mantle of cells; some of these were round or oval and others appeared spindle shaped. At some points these cells were closely packed and at others less so. Their nuclei for the most part corresponded to the shape of the cell. They contained one

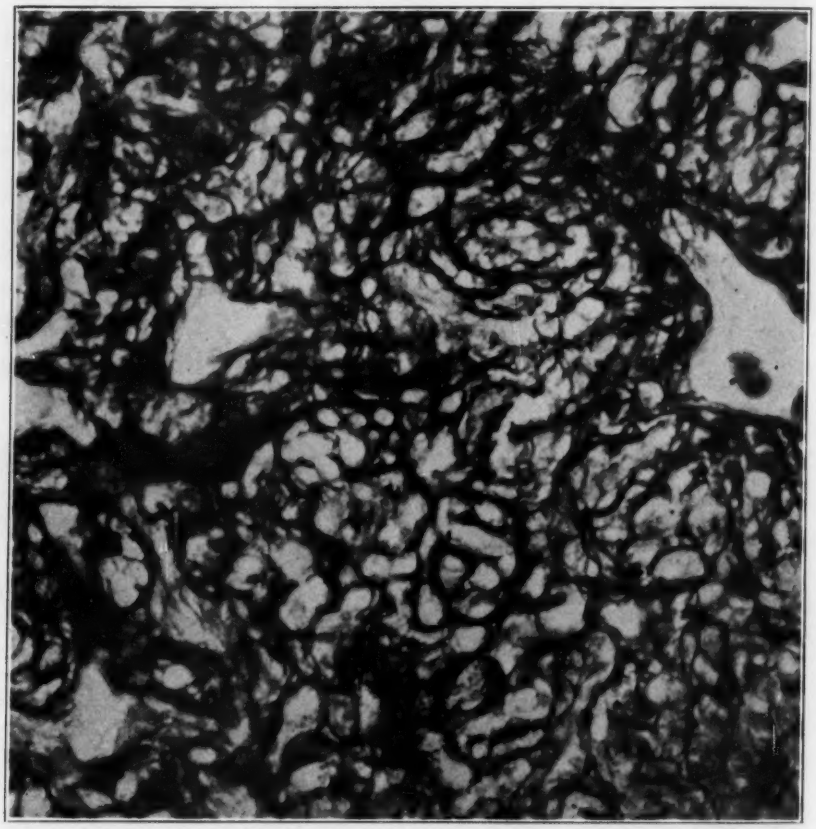

Fig. 3 (case 1).—Reticulum (Laidlaw) stain showing reticulum fibers surrounded by pericytes. × 775.

or more nucleoli and a chromatin network which stained fairly well. The Laidlaw reticulum stain showed that the enveloping cells were outside the reticulum fibers.

Case 2.—This case is interesting because it seems to represent a composite tumor of both pericytes and endothelial cells.

A 12 year old white boy was first seen in the New York Skin and Cancer Unit on Jan. 13, 1945. He complained of a painless growth of six months' duration, located over the left scapula. There had been frequent bleeding, both spontaneous and after slight trauma. The lesion consisted of a solitary firm reddish purple sessile sharply circumscribed nodule. It was 1 cm. in diameter and raised 0.7 cm.

above the surrounding skin. The top was covered with a black crust. A diagnosis of granuloma pyogenicum was made, and the mass was destroyed by electrodesiccation. The patient returned to the clinic ten months later, on October 12. There were multiple recurrences which had been present four months, confined to the area in the vicinity of the original growth. Again, there had been frequent spontaneous bleeding. In a fan-shaped area (fig. 4) approximately 4 cm. in diameter

Fig. 4 (case 2).—Multiple recurrences in area of original growth. Follicular lesions of irritation from adhesive tape are apparent.

were many discrete sharply circumscribed papular lesions, with intervening normal skin. The two largest nodules were at the apex of the fan-shaped area and were contiguous, hemispheric and bright red. They had a cauliflower-like surface covered with a fibrinous purulent exudate. Extending upward and outward toward the left shoulder were thirty to thirty-five fresh lesions, their size varying from that of a pinhead to that of a match head. These were dome shaped, bright red and raised 1 to 2 mm. above the surrounding skin. The satellites became smaller as they extended outward from the original site. Just superior to the largest

nodule there was a bluish scar at the site of the desiccation of the original tumor. Three areas of irritation from adhesive tape were noted, showing follicular papulopustular lesions. A biopsy was performed.

Histologic examination showed, in the upper and middle layers of the corium and in the upper third of the deepest layer, several well defined but irregular masses (fig. 5). One of these was composed of numerous capillaries. These were lined with a single layer of endothelial cells with round nuclei which projected into the lumens of the vessels, some of which were filled with red blood cells. The intervascular stroma was in part normal and in part rather loose and spongy. Scattered throughout the stroma there was a sparse cellular reaction composed of small, round and occasional wandering connective tissue cells. The epidermis above this tumor tissue was rather thin, with obliterated rete pegs and papillary bodies.

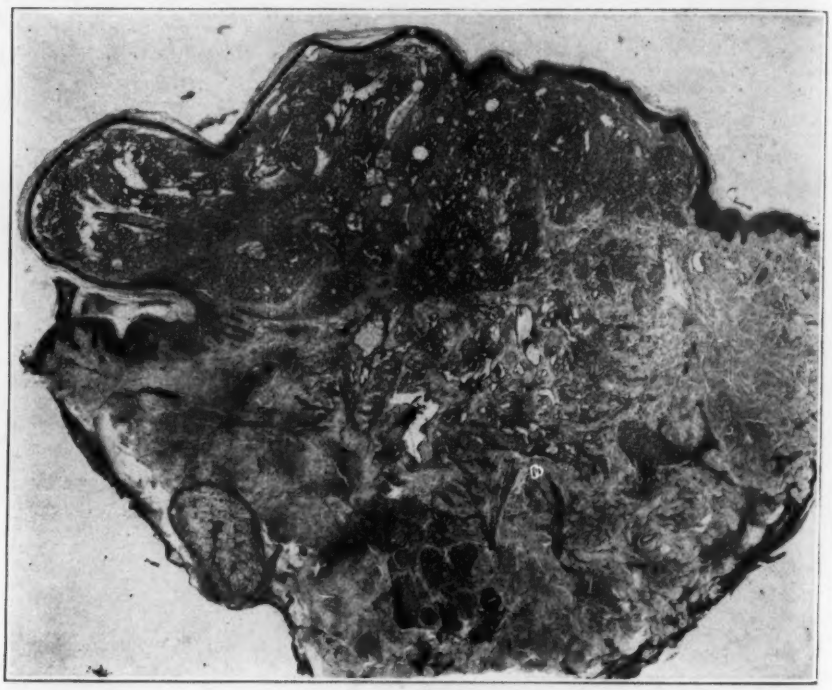

Fig. 5 (case 2).—Photomicrograph of one of the tumor lesions. × approximately 260.

In another part of the section there were several other well defined irregular tumor deposits which, with the low power of the microscope, appeared denser and contained fewer capillaries than in the aforementioned areas. These capillaries were surrounded by a dense mass of cells which appeared to envelop the vessel. With higher magnification (fig. 6) these cells appeared, for the most part, rounded or oval, with a similarly shaped nucleus and a small amount of cytoplasm. Some of the cells were spindle shaped, with a corresponding oblong nucleus. The nuclei of these enveloping cells contained a moderate amount of chromatin and one or several nucleoli. No mitotic figures were visible. Few of the usual inflammatory cells were present. The epidermis above these areas appeared unchanged, and the surrounding collagenous framework revealed no noteworthy changes. With

the Wilder reticulum stain, numerous fine and coarse dark-staining reticulum fibers could be observed. At some points the cells appeared outside and at others inside the reticulum fibers (fig. 7).

On November 8, a piece of tissue was removed for tissue culture and submitted to Dr. Stout and Dr. Murray, together with slides from the biopsy. They concluded that the tumor was of a composite type, composed of pericytes and endothelial cells.

The lesions were treated with three separate exposures of roentgen rays filtered through 2 mm. of aluminum, approximately 425 r being given at each treatment, one month apart. There was complete involution of all vascular lesions, except for some small grouped skin-colored remnant tags. An area of hyperpigmentation about 2 inches (about 5 cm.) square was also noted (fig. 8).

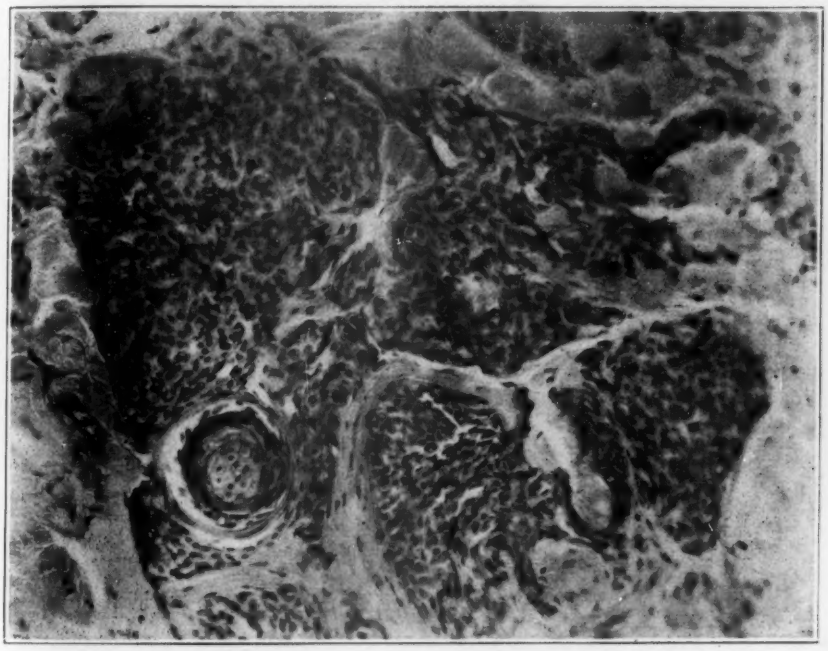

Fig. 6 (case 2).—Photomicrograph of the lesion in figure 5. × approximately 186.

DIFFERENTIAL DIAGNOSIS

Since it is almost impossible to make a diagnosis of hemangiopericytoma clinically and since the diagnosis can be made positively only by microscopic examination, the lesions which it resembles and for which it might be mistaken are described in the following paragraphs.

Granuloma Pyogenicum.—Granuloma pyogenicum usually begins at a point of trauma. It appears as a raised, red to wine-colored, usually pedunculated solitary lesion, with a slightly irregular surface. After removal it may recur, but usually at the original site and never with satellite lesions as in hemangiopericytoma. Histologically granuloma pyogenicum is composed of numerous dilated capillaries of varying

sizes which are separated by a rather loose intervascular stroma, within the meshes of which polymorphonuclear leukocytes, small round cells and wandering connective tissue cells may be observed. The vessels are composed of a single layer of endothelial cells which, at times, may be edematous. No mantles of pericytes are present surrounding the vessels as in hemangiopericytoma.

Angioma.—Angioma usually begins in early life. Its appearance varies from a raised soft raspberry-like lesion to the somewhat bluish deep-seated cavernous type. The lesions vary in size from a pinhead

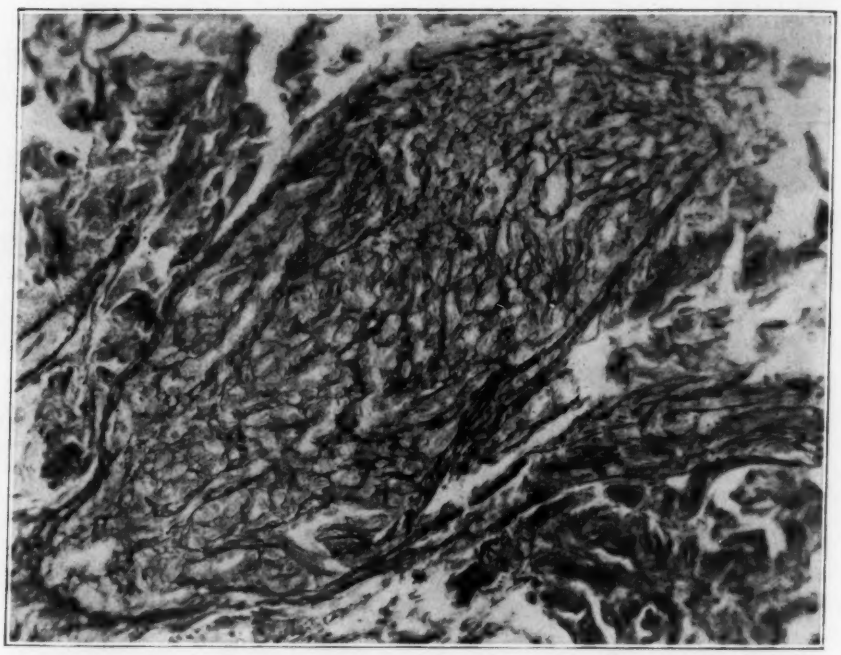

Fig. 7 (case 2).—Wilder reticulum stain of the lesion in figure 5. × approximately 189.

to a walnut or larger. They may be single or multiple. Differentiation can be established on histologic grounds only. Histologically angioma is composed of blood capillaries, the walls of which consist of a single layer of endothelial cells. The supporting connective tissue stroma is fairly close to normal. The capillaries do not have a mantle of pericytes as in hemangiopericytoma.

Lymphangioma.—Lymphangioma is composed of soft opalescent vesicle-like grouped compressible lesions which vary in size from a pinhead to a millet seed and from which lymph may be aspirated. Histologically lymphangioma is composed of lymph capillaries of vary-

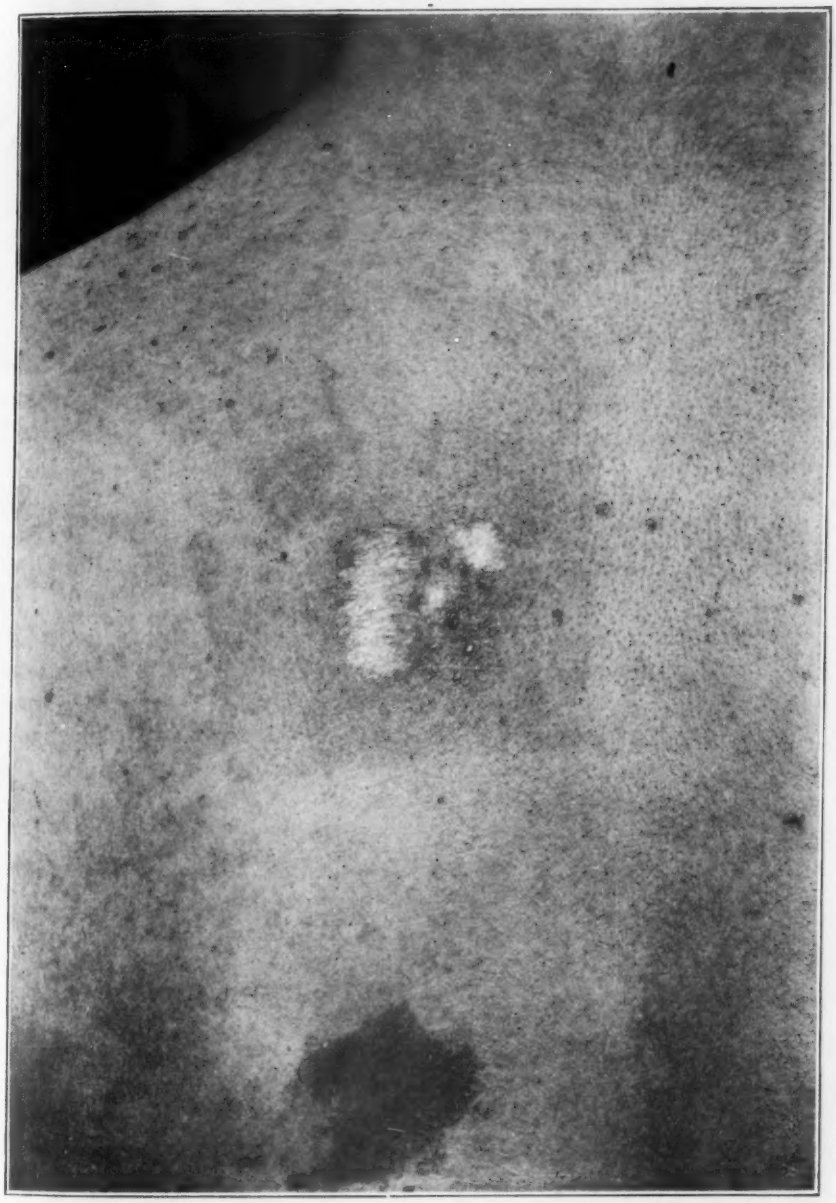

Fig. 8 (case 2).—Involution of satellites and original lesion after filtered roentgen therapy, showing squared area of hyperpigmentation.

ing size. The supporting stroma is fairly close to normal. No mantle of pericytes is demonstrable as in hemangiopericytoma.

Angiosarcoma.—Angiosarcomas may be single or multiple and appear on any part of the body. They are relatively soft and vary in size from a pea to a walnut and at times are larger. Their color may vary from a pale pink to a deep wine red. They are slow growing and not common. Histologically angiosarcoma is a tumor which presumably arises from the perithelial cells of Eberth in the adventitial lymph spaces. It does not arise from the pericytes of Zimmermann. The neoplastic mantle around the cells can be demonstrated to be composed of the former rather than the latter.

Glomus Tumor.—Glomus tumor is usually a solitary bluish somewhat firm lesion which varies in size from a pinhead to a small pea. It occurs most commonly on the extremities and is associated with considerable pain and tenderness. It does not commonly recur after excision. Histologically glomus tumor is composed of a more or less typical structure similar to the normal glomus. The most prominent change is the proliferation of the so-called epithelioid cells. According to Stout and his co-workers the epithelioid cells are pericytes. While hemangiopericytoma presents a hyperplasia of pericytes it does not have the structure of a glomus.

Hemangioendothelioma.—Hemangioendotheliomas may cause some difficulty in differentiation from a hemangiopericytoma, particularly from a clinical standpoint. They may be solitary or multiple and may vary in size from a pea to a lemon. They are fairly soft, are usually burgundy red in color, bleed easily, may ulcerate and may be surrounded by satellites. They may occur on any part of the body and are most frequently observed in children. Histologically hemangioendothelioma is a tumor composed of neoplastic endothelium. Neoplastic endothelium may proliferate within the lumen of the vessel, may invade the vessel wall or may proliferate outside the wall. However, endothelial cells, of which the tumor is composed, retain their histologic appearance, and they do not have the characteristics of pericytes. In hemangiopericytoma the endothelium is composed of normal endothelial cells which never invade the vessel wall.

SUMMARY AND CONCLUSIONS

The hemangiopericytoma is a vascular tumor characterized by the formation of endothelial tubes and sprouts, with a surrounding sheath of rounded and sometimes elongated cells. They are derived from the capillary pericytes described by Zimmermann. The pericyte of Zimmermann has been shown to be the origin of the enveloping mantle of cells in the glomus tumor, the hemangiopericytoma and the cutaneous and subcutaneous leiomyomas. Diagnosis is difficult to establish on

clinical grounds, but on histologic grounds the diagnosis can be made with the aid of hematoxylin and eosin stain, Wilder reticulum stain or Laidlaw stain and tissue culture. It is possible to have a blood vessel tumor composed both of pericytes and endothelial cells.

In our case of a composite tumor roentgen irradiation appeared to be of definite value, but it is too early to comment on the permanency of the result. For this reason and because of the danger of recurrence and especially metastasis, wide scalpel excision is the probable therapeutic method of choice.

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EXTRACELLULAR CHOLESTEROSIS WITH PULMONARY INVOLVEMENT

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EXTRACELLULAR cholesterosis is a rare chronic systemic disturbance of lipid metabolism in which, for some as yet unknown reason, cholesterol finds its way into the tissues causing a definite clinical and histopathologic picture.

Urbach [1] investigated and reported the first case of this disease and also named it. This case had previously been described by Kerl [2] and subsequently was again reported by him.[3] Search of the literature does not show any other report until that made by Laymon.[4] Two cases in which the condition resembled this disease were reported by Levin,[5] and Frost and Anderson,[6] but the diagnoses were never fully confirmed. Rosen [7] had a patient under observation for many years who presented the chief features of this condition. It is our impression that there have been other examples of this disease which were unrecognized.

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology, New York Post-Graduate Medical School and Hospital (Dr. Marion B. Sulzberger, Director).

1. (*a*) Urbach, E.; Epstein, E., and Lorenz, K.: Beitrage zu einer physiologischen und pathologischen Chemie der Haut: Extrazellulare Cholesterinose, Arch. f. Dermat. u. Syph. **166**:243-272, 1932. (*b*) Urbach, E.: Lipoidstoffwechselerkrangungen der Haut, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1932, vol. 12, pt. 2, pp. 320-330; (*c*) Kutane Lipoidosen, Dermat. Ztschr. **66**:371-386, 1933.

2. Kerl, W.: Multiple Knotenbildung, Reichlich Lipoidenthaltend, Zentralbl. f. Haut- u. Geschlechtskr. **36**:37, 1931.

3. Kerl, W.: Ueber eine neuartige generalzierte Lipoid-Infiltration mit Vorwiekender, zum teil Knotenformiger Beteiligung der Haut und Schleimhaut, in Neisser, A., and Jacobi, E.: Ikonographia Dermatologica, Berlin, Urban & Schwarzenberg, 1932.

4. Laymon, C. W.: Extracellular Cholesterosis, Arch. Dermat. & Syph. **35**:269-284 (Feb.) 1937.

5. Levin, O. L.: A Case for Diagnosis (Extracellular Cholesterosis?), Arch. Dermat. & Syph. **44**:733 (Oct.) 1941.

6. Frost, K., and Anderson, C. R.: Extracellular Cholesterosis of Urbach, Arch. Dermat. & Syph. **39**:1061 (June) 1939.

7. Rosen, I.: Personal communication to the author.

REPORT OF A CASE

A. C., a white married woman, aged 23, born in the United States, was first seen at the New York Skin and Cancer Unit Jan. 16, 1948. The patient presented an eruption which began in March 1947, at which time she was pregnant five months. The eruption first appeared on the knees in the form of several painful "red bumps." In June similar changes developed on the buttocks, and by October new lesions appeared gradually in the following sequence: legs, over the interphalangeal joints

Fig. 1.—Extensive brownish blue discoloration, with thickening and slight scaling of the skin. Nodules show superficial necrosis.

of the fingers and toes, elbows, thighs and left side of the neck. At this time, after an intratracheal study with iodized poppyseed oil, all the affected sites increased in size, severity and tenderness, and many ulcerated within a short time. With the exception of the affected areas on the thighs, buttocks and neck, there was no tendency toward spontaneous healing.

There was no history of serious illness until the age of 13. After a tonsillectomy, a productive cough developed, which had been present almost continuously. The

patient's only pregnancy, previously mentioned, terminated normally in a healthy child. The familial history on both sides did not reveal a similar cutaneous condition or metabolic disorder.

The patient was first treated for the cutaneous complaint by her family physician who gave a diagnosis of erythema multiforme. There was no improvement with topical treatments, internal therapy or 1 skin erythema unit of roentgen rays given over a period of four weeks. On Oct. 8, 1947, she was hospitalized for two weeks at Newark, N. J., because of the exacerbation of the cutaneous disease and loss of weight, fever and severe cough. From a biopsy specimen taken at that time from a lesion on the buttock the diagnosis was erythema multiforme with secondary pustu-

Fig. 2.—Nodules on knuckles.

lation. The roentgenologic observations, including those in studies with iodized poppyseed oil, suggested the possibility of pulmonary tuberculosis, although on clinical grounds other diagnoses were considered. Roentgenograms of the hands showed them to be normal. Repeated examinations of the sputum and gastric washings failed to show tubercle bacilli. At the hospital she received 20 Gm. of streptomycin in divided doses, which improved the pulmonic symptoms, but not the cutaneous disease.

On the patient's admission to the New York Skin and Cancer Unit the cutaneous observations were limited to the dorsa of the fingers and toes, elbows, knees, legs, ankles, back of the thighs, buttocks and left side of the neck. The mucosae were not affected. On the left side of the neck, thighs and buttocks the lesions had healed with coin-sized, irregularly shaped, superficial pigmented scars. Both legs

showed extensive brownish blue discoloration, with thickening and slight scaling of the skin (fig. 1). Lesions about one to two weeks old on the ankles consisted of elevated firm brownish blue papules and nodules, split pea to quarter size, exquisitely painful on pressure. Well advanced nodular lesions present on the legs were foul-smelling and necrotic; some showed deep ulcerations and others a black crust. On the knuckles (fig. 2) and toes there were present dime-sized to nickel-sized sharply circumscribed moderately elevated firm reddish yellow nodes; the surfaces of these were uneven and scaly and had undergone superficial necrosis. On the elbows and knees there was noted a plaquelike formation, consisting of coalesced papules and nodules, some assuming annular shapes.

On physical examination the patient appeared somewhat pale, underweight and frail. Except for the described lesions positive observations were confined to the chest: dulness over both upper lobes with diminished breath sounds and many coarse moist rales; a few were also present at both bases. The liver and spleen were not palpable, and there was no adenopathy. Eye ground observations were normal.

Laboratory Observations.—The blood cell count on Jan. 28, 1948, showed: red blood cells 5,830,000, hemoglobin 12.5 Gm. per hundred cubic centimeters, white blood cells 17,750, with 75 per cent polymorphonuclear neutrophils, 1 per cent polymorphonuclear eosinophils, 17 per cent lymphocytes and 7 per cent monocytes. Pronounced achromia, anisocytosis and poikilocytosis were noted. The differential count on February 24 showed 18,000 leukocytes, 71 per cent polymorphonuclear neutrophils, 1 per cent polymorphonuclear eosinophils, 12 per cent lymphocytes, 5 per cent monocytes and 11 per cent band forms. The sedimentation rate was 25 mm. per hour (normal 15 mm. per hour). The basal metabolic rate on February 1 was —12 per cent. Two separate blood serologic tests for syphilis elicited negative reactions. Urinalysis showed no abnormalities; with polariscopic examination no double-refractile bodies were found. On Jan. 23, studies of the chemical content of the blood were: total lipids, 337 mg. (normal 500 to 700); fatty acids, 249 mg.; cholesterol, 90 mg. (normal 160 to 230), of which 35 per cent consisted of cholesterol esters; nonprotein nitrogen, 24 mg.; urea, 8.5 mg.; creatinin, 1 mg., and sugar 70 mg. per hundred cubic centimeters. On February 6, total cholesterol was 120 mg. per hundred cubic centimeters, of which 50 per cent were cholesterol esters. On February 6, tests of hepatic function showed: cephalin flocculation 1 plus (doubtful), thymol turbidity 3 units (normal) and galactose tolerance normal.

Reactions to intradermal tests with old tuberculin in 0.1 cc. doses, ranging from 1:1,000,000 to 1:100 dilutions, were negative. The reactions to intradermal tests to coccidioidin and histoplasmin antigens were negative. Smears, cultures and guinea pig inoculations of the sputum failed to show tubercle bacilli. Direct mount and culture revealed no pathogenic fungi. Chemical examination of the sputum showed 57.1 mg. of cholesterol per hundred cubic centimeters; double refractile bodies were present on polariscopy.

Roentgen examination of the chest (fig. 3) showed both lung fields to contain predominantly productive infiltrations which were partly confluent in the first right intercostal space. Several small nodular shadows were seen in both upper lung fields, the largest one underlying the fourth left anterior rib, measuring 1 cm. in diameter. Roentgen examination of all bones of the upper and lower extremities revealed them to be essentially normal.

Chemical examinations for cholesterol in the excised skin were made by the Sperry-Schonheimer acetone-alcohol method. On February 26, a large piece of affected skin was removed from the right knee, trimmed of subcutaneous fat and analyzed. The laboratory reported: total cholesterol, 1.51 mg. (wet tissue), free

cholesterol 1.28 mg. and cholesterol esters 0.23 mg. per hundred cubic centimeters. Polariscopic examination showed no double refractile bodies. On February 29, a piece of apparently normal skin from a nonaffected area on the chest of the patient was excised and reported as containing: total cholesterol, 0.76 mg.; free cholesterol, 0.60 mg., and cholesterol esters, 0.16 mg. per hundred cubic centimeters. On March 18, a piece of skin from a normal person was removed and showed: total cholesterol, 0.67 mg.; free cholesterol, 0.42 mg., and cholesterol esters, 0.25 mg. per hundred cubic centimeters.

Histologic Studies.—A well advanced nodule removed from the right knee was examined by Dr. Charles F. Sims, who reported as follows: The hematoxylin and eosin stain revealed that almost the entire cutis was the seat of a massive cellular infiltrate (fig. 4). This process was more intense toward the epidermis, shading

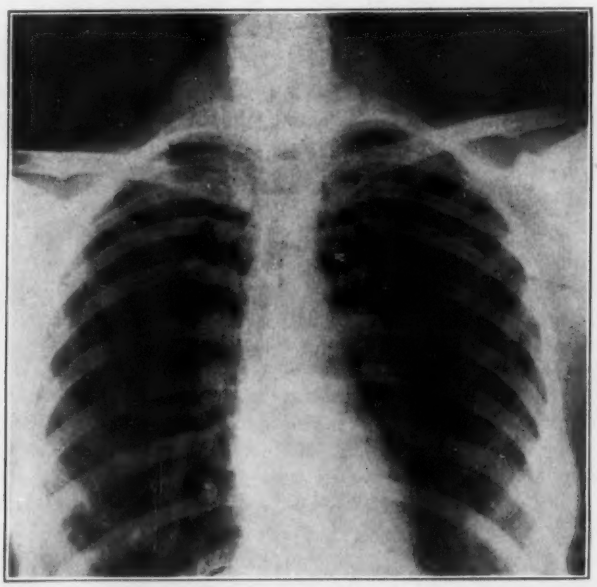

Fig. 3.—Roentgenogram showing infiltration of both lung fields.

off into the deep cutis. The connective tissue framework was almost indiscernible and appeared homogenized with intense red, particularly in the upper part of the corium. The elastic tissue (Weigert's stain) was practically nonexistent in the heavily infiltrated areas. The cellular infiltrate was made up mainly of enormous numbers of polymorphonuclear leukocytes, together with lymphocytes, round cells, wandering connective tissue cells and fibroblasts. No giant or foam cells were noted. There was fragmentation of nuclei. The tissue spaces were packed with these cells, especially around the coil glands. Scattered throughout the reaction were many dilated and congested blood vessels with swollen endothelium. The density of the infiltrate obscured the perivascular reaction; in places, the vessels were surrounded by lakes of edema and fibrin. The epidermic changes were not distinctive, merely showing flattening and slight disorganization in the cells of the basal layer. Sudan III stain did not reveal the outright bright orange noted in pronounced lipid infiltration, but conveyed the impression of the presence of great amounts of extracellular amorphous material mainly in the upper and middle parts

of the cutis. With the Liebermann-Borchard differential stain for cholesterol these same areas showed a positive staining reaction. Perles' stain for iron-containing pigment revealed no abnormalities.

Course of Illness.—For the first four weeks of observation the lesions on the hands, feet, elbows and knees remained stationary. Those on the legs coalesced and spread, finally forming huge painful, necrotic, foul-smelling ulcerations (fig. 5), causing the patient to be bedridden. During this period fresh lesions appeared on the ankles and sides of the knees.

On February 15, a diet completely free of animal fat was instituted. After that no new eruption appeared and pain diminished; a tendency toward healing, espe-

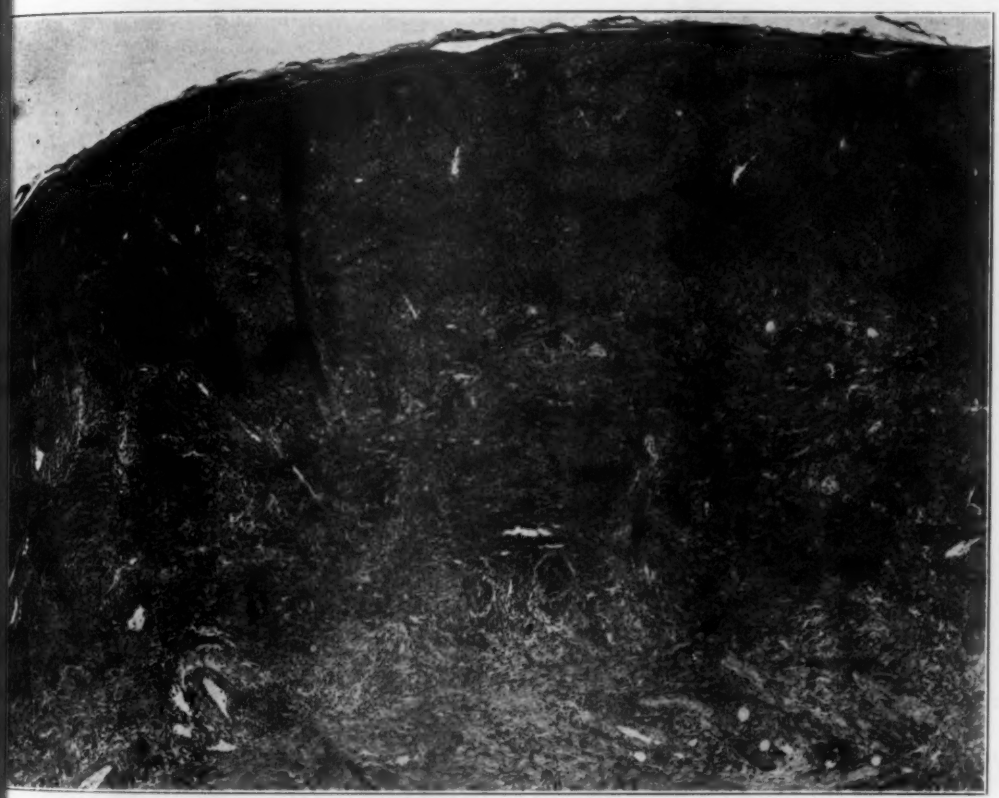

Fig. 4.—Low power microphotograph showing massive cellular infiltrate and absence of foam or giant cells.

cially in the large ulcerated lesions, was noted, with an increased feeling of well-being as shown by the voluntary elimination of sedatives, better appetite and improved morale. A test dose of 100 r applied to an area on the fingers resulted in substantial improvement. The patient also received at various times injections of crude liver extract, high vitamin therapy, thyroid and iron, but without appreciable effect.

DIFFERENTIAL DIAGNOSIS

The most important dermatosis to be considered is, first, xanthomatosis (multiplex tuberosum type). In xanthoma clinically, the lesions

are more yellow and painless, usually lack inflammatory changes and do not ulcerate. Microscopically the intracellular phagocytosis, as evidenced by foam and giant cells and a noninflammatory reaction, are noted. Study of the chemical content of the blood shows hyperlipemia. The rare type, xanthoma areolare multiplex (Riehl and Arzt) is difficult

Fig. 5.—Photograph showing severity and extent of ulceration.

to differentiate clinically from extracellular cholesterosis, but the histologic picture is that of xanthoma.

Eruptions due to halogen drugs can be differentiated only by the characteristic disturbance of lipid in the blood and tissues. At times a history of drug intake is helpful.

With erythema multiforme of comparable severity the patient is febrile; the lesions are not greatly infiltrated; it is more acute and runs a much shorter course. In general, granuloma annulare lesions do not ulcerate, are painless and indolent and have a typical histologic picture.

Idiopathic hemorrhagic sarcoma of Kaposi may simulate extracellular cholesterosis. Absence of lipid deposition, normal blood lipid content, a different histologic appearance and a positive reaction to Perles' stain occur in the former.

COMMENT

As in Urbach's description of extracellular cholesterosis, our patient showed a diminished total lipid and low cholesterol content of the blood serum, increased free cholesterol in the diseased tissue (three times that of a normal control) and a distinctive clinical and histopathologic picture. In Urbach's case the systemic nature of the disease was evidenced by some hepatic insufficiency and splenomegaly, while in our case there was pulmonic involvement, as demonstrated by the physical observations, the roentgenogram of the chest and especially the double refractile bodies and the high cholesterol content in the sputum.

Whereas Urbach showed that ingestion of cholesterol caused an immediate severe exacerbation of the lesions, we found a similar dietary cholesterol relationship by evident and decided improvement in the cutaneous lesions and general condition of the patient soon after she was put on an animal-fat-free diet, which contained practically no cholesterol.

To explain the pathogenesis of the disease, Urbach considered three possible mechanisms. He discarded the first two, namely, (1) a reticuloendothelial cause and (2) an infectious or inflammatory cause. He subscribed to the third theory, that all the features of the disease resulted from a primary disturbance of lipid metabolism. Laymon agreed with this view, as we do also, because our patient was afebrile at all times; there was no adenopathy or splenic involvement, and except for moderate leukocytosis, the hemogram was not indicative of any abnormal state of the reticuloendothelial system. Also, Laymon pointed out the absence of such pronounced lipid changes in any known infectious or inflammatory disease. We would like to note here that inception of the cutaneous condition in our patient occurred during her pregnancy, at a time when there is a known physiologic change in cholesterol metabolism.

Rational speculation along pathogenetic lines as to the cause of this lipid disturbance might well be started here by mentioning an investigation that was done for us by Dr. Herman Sharlit on the patient's blood serum. He corroborated the previous observations of decidedly diminished blood lipid content, including a low cholesterol content. By his special method [8] he demonstrated in vitro that even though there was

8. Sharlit, H.: The Production and Measurement of Colloid Clouds in Alcoholic Solutions of Blood Serum Lipids, J. Invest. Dermat. **5**:389 (Dec.) 1942.

present a diminished amount of cholesterol, the blood serum of this patient was unable to absorb appreciable additional amounts of cholesterol as does normal serum, without the lipids breaking out of their emulsified state. This led him to express the belief—especially with our own observation that ingested cholesterol makes the condition clinically worse—that in vivo, too, the blood for some reason is unable to hold normal amounts of cholesterol in suspension and it is hence deposited in the tissues. It is the opinion of many investigators that the lecithin and cholesterol ester fractions of the total lipid may have to do with normal cholesterol blood suspension. Thannhauser,[9] in mentioning the action of the body on cholesterol, pointed out that the liver and circulating blood are important sites for the cholesterase transformation of cholesterol into its esters. Therefore, any disturbance in this enzymatic system would tend to fall in with the previous theoretical consideration. We expect to treat the patient with other lipid fractions, e. g., lecithin orally, to note if there is any effect on the ability of the patient's blood to maintain normal cholesterol suspension.

The next problem is the peculiar histopathogenesis that results when this precipitated cholesterol, after damaging the blood vessel—as so well shown by Urbach—seeps out into the tissues. This is totally different from the picture seen in xanthomatosis, in which there is also a similar deposition of cholesterol in the skin. We can explain this different reaction in extracellular cholesterosis only by the failure on the part of the tissue to metabolize the cholesterol, as in xanthomatosis, setting up instead a severe inflammatory response to a foreign body of irritative and toxic nature.

CONCLUSIONS

A typical example of the disease extracellular cholesterosis as described by Urbach, with the additional systemic feature of pulmonic involvement, is described.

As done previously only in Urbach's exhaustive studies, chemical determinations of skin cholesterol were carried out and are reported.

We have suggested the two possible causes for the clinical symptoms, namely: (*a*) an inability of the blood to sustain normal levels of cholesterol and (*b*) an unusual inflammatory response of the skin to the cholesterol deposited in the tissues as a result of the aforementioned failure.

This is a preliminary report. Further experimentation is being undertaken to find out the factors which cause such cholesterol precipitation and studies made of the response of normal and diseased animal and human skin to the introduction of cholesterol intradermally.

Dr. M. Bruger and Miss E. Goldman of the Department of Chemistry, New York Post-Graduate Hospital, gave assistance in this work.

124 East Fortieth Street.

9. Thannhauser, S. J.: The Lipoidoses, New York, Oxford University Press, 1940, p. 18.

LEUKODERMA PRODUCED BY ANTIOXIDANTS

Report of Cases

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THE PURPOSE of this paper is to present additional cases of leukoderma produced by antioxidizing agents contained in manufactured articles. The chemistry of rubber and rubberized industries has developed not only along lines of greater production of synthetic products but also toward extending the aging of these goods. For this latter objective, the chemical compound "agarite alba," the trade name for monobenzyl ether of hydroquinone, an antioxidant of pigment, is usually added. This observation was first established by Oliver, Schwartz and Warren.[1] These authors observed in the tanning industry occupational leukoderma in men wearing rubber gloves which contained this antioxidant to help the aging of rubber. Another observation was made of occupational leukoderma in a woman employed to wash contraceptive diaphragms in a gynecologic laboratory.[2]

REPORT OF CASES

CASE 1.—E. B., a man aged 29, consulted me because of the appearance of white patches on the hands. These had been increasing in size and number for the two months prior to examination. He was employed by a firm the business of which was to cover metal objects with a rubber compound. His particular duties were to immerse wire dish tray holders into this compound. He had been doing this for about two years, but only for two or three months prior to examination had he noticed the appearance of white spots on his hands. The only discomfort experienced was a warm feeling in his hands in the evening, after work. This feeling, he stated, did not occur over the week end, when he did not work.

Examination showed absence of pigment in patches involving the fingers of both hands (fig. 1). This was especially noticeable on and between the fifth, fourth, third and index fingers. On the dorsum of the hands there were a few discrete pinhead-sized to pea-sized leukodermic macules. There were no erythematous or scaling lesions noticeable. Also on the forearms there were a few pea-sized leukodermic spots. A patch test performed on the arm with the rubber compound and left in place for four days gave a positive result, in that a small pea-sized leukodermic spot was observed. The particular firm in question gave the

1. Oliver, E. A.; Schwartz, L., and Warren, L. H.: Occupational Leukoderma, Arch. Dermat. & Syph. **42**:993 (Dec.) 1940.

2. Spencer, G. A.: Pigmentogenesis, J. Nat. M. A. **36**:43, 1944.

information that for the past three months 1 per cent of the chemical agent "agarite alba" had been added to the rubber compound. The rest of the examination revealed nothing abnormal.

Fig. 1.—Leukoderma involving fingers of both hands.

Fig. 2.—Discrete leukodermic spots on and between the fingers.

CASE 2.—B. B., a man aged 26, brother to E. B., consulted me at the same time for a similar absence of pigment on the hands. He noticed the condition of his hands for three months. He was also employed by the same firm, and his special

Fig. 3.—Rectangular leukodermic area on the side of face.

Fig. 4.—Leukodermic area on the inner aspect of the leg and the foot.

duties were to take the dipped trays from his brother and to wash them in water. In his case there were no subjective symptoms.

Examination showed discrete pinhead-sized to pea-sized leukodermic spots on the dorsal surface of both hands. A few such spots were seen in the webs of the fingers (fig. 2). Also, on the glans penis there was a pea-sized spot, probably a self-imposed patch test. No erythematous or scaling lesions were noticeable. A patch test of the compound, performed on the arm and left for four days, gave a positive result, in that a small pea-sized leukodermic spot was observed.

Case 3.—A woman aged 30 was seen by me for absence of pigment which had appeared on the face and on the left leg. She stated that she had been hospitalized for an acute infection of the upper part of the respiratory tract and a sprained left ankle. During her stay of three weeks in the institution, her ankle was strapped

Fig. 5.—Bandlike leukoderma on the forehead, corresponding to contact of the hat band.

with adhesive tape and oxygen therapy was administered for the pulmonary condition. The nasal catheters were kept in place for a few days by means of adhesive tape. On returning home she noticed the condition of her face and ankle.

Examination showed leukodermic areas on both sides of the face. On the right side there were two well defined patches devoid of pigment, each about 4 inches (10 cm.) in length and ½ inch (1.3 cm.) in width. One of these patches was rectangular in shape (fig. 3). On the inner aspect of the left leg there was a well defined almost rectangular area of leukoderma, about 10 inches (25 cm.) in length, extending from the arch over the external maleolus and up to the inner aspect of the left leg (fig. 4). The rest of the body showed nothing abnormal. A patch test performed with adhesive tape and left in place for four days gave a positive result with a leukodermic area corresponding to the size and shape of the patch. It was not possible to learn the nature of the antioxidant used in the manufacture of the tape.

CASE 4.—A. G., a man aged 40, a postal employee, was seen by me for an eruption involving the forehead and scalp (fig. 5). He stated that he had bought a regulation cap and after wearing the cap for a week experienced a slight burning sensation of the scalp.

Examination showed leukodermic areas on the forehead and in the parietal and occipital regions of the scalp corresponding to the contact with the band of the cap. A patch test performed with a piece of the band and left in place for four days gave a positive reaction with a leukodermic area. The band consisted of compressed paper that was processed. It was not possible to ascertain the exact chemical constituents of the compound.

SUMMARY

Cases of leukoderma produced by antioxidizing agents are reported. One such antioxidizing agent is "agarite alba," trade name for monobenzyl ether of hydroquinone.

129 West One Hundred and Twenty-Ninth Street.

ACUTE RECURRENT PUSTULAR BACTERID

Report of a Case

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AS EARLY as 1920, Bloch stated his belief in the existence of secondary eruptions from foci of infections produced by many different types of micro-organisms and he suggested the inclusive name "microbids" for such eruptions, whether due to cocci, fungi, viruses or other infectious agents.

Later, in 1934, Andrews, Birkman and Kelly [1] described a group of "recalcitrant pustular eruptions of the palms and soles" in 15 patients and differentiated them from similar eruptions by certain criteria. Andrews and Machacek,[2] in 1935, confirmed and expanded the preceding report. In a third paper, in 1941, Andrews and Barnes [3] analyzed 200 cases of recalcitrant eruptions of the palms and soles and found twenty-four "pustular bacterids" among them. Finally, in the latest edition of his textbook (1946)[4] Andrews gave the most recent résumé of the pustular bacterid.

According to these descriptions the eruption is of a chronic character with acute exacerbations, sometimes lasting for many years, beginning with vesicles and pustules in the middle portions of the palms and soles and soon extending outward, especially to the lateral surfaces. If there are vesicles they soon become pustular and hemorrhagic puncta also become visible. In the later stages some crusting and characteristic adherent scaling develop. The lesions are sometimes unilateral; usually, however, they break out symmetrically, or successive crops show symmetric distribution. They heal by drying up and scaling off. Their differential diagnostic characteristics are: (1) culturally sterile pus (in contrast to Hallopeau's acrodermatitis continua and to dermatitis repens as well as to dermatophytosis, secondarily infected dyshidrosis, pompholyx and vesiculopustular dermatitides); (2) almost always

From the Dermatologic Section, Fitzsimmons General Hospital, Denver.

1. Andrews, G. C.; Birkman, F. W., and Kelly, R. J.: Recalcitrant Pustular Eruptions of Palms and Soles, Arch. Dermat. & Syph. **29**:548-563 (April) 1934.

2. Andrews, G. C., and Machacek, G. F.: Pustular Bacterids of the Hands and Feet, Arch. Dermat. & Syph. **32**:837-847 (Dec.) 1935.

3. Andrews, G. C., and Barnes, M. C.: Pustular Bacterids and Allied Conditions, South. M. J. **34**:1260-1266 (Dec.) 1941.

4. Andrews, G. C.: Diseases of the Skin, ed. 3, Philadelphia, W. B. Saunders Company, 1946, pp. 262-264.

detectable infectious foci, usually abscessed tonsils, sometimes infected teeth, the removal of which is followed by healing of the eruption, which otherwise is recalcitrant to all treatment; (3) characteristic histologic changes (deep-seated epidermal pustules with acanthosis) that differentiate the disease from psoriasis, the existence of which should be excluded, and (4) positive allergic cutaneous reactions with vaccines from pyogens.

Fig. 1.—Vesiculopustular and hemorrhagic eruption of the palms and wrists.

If these criteria are applied strictly, then the pustular bacterid is uncommon. The following case is, in my opinion, a good example of the disease.

REPORT OF A CASE

R. K., a 27 year old white veteran, was admitted to the hospital on May 19, 1946. His previous history was essentially noncontributory. In the previous seven months he had had three or four attacks of acute tonsillitis, and simultaneously there developed "blisters" on the feet, ankles, legs, knees and hands. After the tonsillitis had subsided the cutaneous lesions dried up and healed within about one week.

Ten days before admission a sore throat recurred. Three days later lesions began to break out on the palms and soles.

On admission the patient had a temperature of 102.4 F. Both tonsils were moderately enlarged and reddened, and showed a number of small follicular abscesses. The regional submaxillary lymph nodes were distinctly palpable, rather soft

Fig. 2.—Vesiculopustular and hemorrhagic eruption of the left sole and of the toes.

and somewhat tender. There were no other abnormal physical observations excepting the rash.

The patient presented a generalized eruption of vesiculopustular and hemorrhagic character (figs. 1 and 2). The skin of the arches and the adjacent medial surfaces of the feet, the middle portions and the thenar eminences of the palms and the volar aspects of the wrists were studded with numerous discrete lesions, most of which were pustular. Lesions of the same kind also appeared on the plantar sur-

faces of the toes, a few on the volar and lateral sides of the fingers, some more on the legs, and scattered vesicles and pustules on the thighs, on the upper extremities and on the entire trunk. The scalp, face and neck were free of lesions. There was no lymphangitis or lymphadenitis.

The white blood cell count showed 14,200 leukocytes, with 72 per cent neutrophils. The red cell count and the urine were normal. The Kahn reaction was negative.

Direct examination of the pus and vesicle fluid from the cutaneous lesions revealed no mycelia or spores, and there were none in the tops of the vesicles from the toes. Repeated examinations were made. Cultures on Sabouraud's agar remained sterile. Gram stains for bacteria gave likewise negative results, and cultures for pyogenic organisms produced no colonies. However, hemolytic streptococci could be seen in stained smears, and grew in cultures, from the pus of the abscessed tonsils.

In the first few days the patient received potassium permanganate baths and the hands and feet were soaked in solution of aluminum acetate. After the laboratory observations had been obtained, on May 27, the patient took 1 Gm. of sulfadiazine six times a day for four days (initial dose 2 Gm.). During this time the throat infection cleared up and the cutaneous lesions began to dry; there developed some crusting and scaling, and within about one week after the beginning of the treatment with sulfonamide drugs there was only slight scaling left. No new lesions had developed after the start of sulfadiazine therapy.

Then a tonsillectomy was advised by the eye, ear, nose and throat section, and the patient promised to have this operation performed with the next few weeks. Unfortunately, contact with him was lost after his discharge from the hospital.

COMMENT

The simultaneous occurrence of the streptococcic tonsillitis and the cutaneous eruption, the sterility of the cutaneous lesions and the prompt healing of the rash coincident with the spontaneous regression of the sore throat, or after sulfadiazine therapy, all were factors that made the case unusually interesting. It is to be regretted that permanent cure after tonsillectomy was not observed because the patient was lost to observation after he left the hospital. Such a result could have been confirmatory evidence of Andrews' concept. However, the case seems clear enough, even without the "crucial test," and it might, therefore, contribute to the recognition of the dermatosis.

SUMMARY

A 27 year old white man showed repeated streptococcic sore throats and simultaneous vesiculopustular eruptions of the palms and soles. Bacteriologic and fungus examinations, including cultures, of the cutaneous lesions showed negative results. The cutaneous rash healed spontaneously after the regression of the tonsillitis after sulfadiazine therapy. The case may serve as evidence for the existence of the "pustular bacterid."

35 Fort Washington Avenue.

VIOFORM IN DERMATOLOGIC THERAPY

With Particular Reference to Its Use in Different Vehicles

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AND
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THE QUINOLINE derivative known as "vioform" (5-chloro-7-iodo-8-hydroxyquinoline) has been extensively used internally for the treatment of amebic dysentery. Although European dermatologists [1] have long recognized the value of "vioform" in the external treatment of skin diseases, the usefulness of this compound in external dermatologic therapy has not yet received full recognition in the United States. Only a few references [2] can be found in the literature of this country. It was not until 1944 that the "New and Nonofficial Remedies" of the Council on Pharmacy and Chemistry of the American Medical Association included the mention of the external therapeutic use of "vioform".[3]

The mode of "vioform's" therapeutic action is not known, and the indications and value of the drug have been established almost exclusively on an empiric foundation.

Subsequent to the completion of the present report a note on the use of "vioform" in local therapy appeared in THE ARCHIVES (Saunders, Thomas S.: The Use of Vioform in Local Dermatologic Therapy, Arch. Dermat. & Syph. **54**:456 [Oct.] 1946). The publication of Saunders' note impels us once more to call attention to the fact that the usefulness of vioform in external treatment is not a notion on our part, but is founded on many decades of experience on the part of a great number of competent dermatologists and is based on observations in at least tens of thousands, and probably hundreds of thousands, of cases. While differences of opinion not only "make hoss racin'" but often also make for progress in medicine, it seems regrettable that a publication should appear in which a dissenting opinion is based on only 14 cases. Perhaps if Dr. Saunders had had more experience or if more details of Dr. Saunders' experience were available, it would be possible to discover the causes for his unfavorable impressions.

1. Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Vol. V/1, Berlin, Julius Springer, 1930, vol. 5, pt. 1.

2. Wise, F., and Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, Ill., The Year Book Publishers, Inc., 1942. Sulzberger, M. B., and Wolf, J.: Dermatologic Therapy in General Practice, ibid., 1942. Pillsbury, D. M.; Sulzberger, M. B., and Livingood, C. S.: Manual of Dermatology, Philadelphia, W. B. Saunders Company, 1942.

3. New and Non-Official Remedies, Chicago, American Medical Association, 1944.

Based on personal experience which extends over twenty years and on direct observations which include several thousand cases, we believe that the most important indications for the external application of "vioform"-containing preparations are as follows:

1. Dermatoses and infections in which a mild antibacterial and antifungous effect is desired and in which irritant action must be reduced to an absolute minimum (paronychias, secondarily infected herpes simplex, erosio interdigitalis, impetigos), i. e., dermatoses due to superficial infections or which have been irritated by previous therapy or by other factors and in which other local antiseptic agents, such as mercury, resoricinol, iodine, penicillin and sulfonamide drugs, are contraindicated, not tolerated or not effective.

2. Eczematous eruptions in acute, subacute or chronic stages, and particularly in nummular eczemas, in impetiginized or infected eczemas of the hands or other parts and in eczematized superficial infections. In these conditions the "vioform" application can be used alternately with soothing and antiseptic and antieczematous wet compresses, tinctures or lotions or can replace these when they are not feasible, not effective or not tolerated.

3. Atopic dermatitis, when other commonly used agents have failed or have caused aggravation and particularly in areas with eczematization and superficial infection due to scratching or other causes.

4. Psoriasis, particularly in irritated and pruritic areas and areas with secondary superficial dermatitis, maceration and eczematization, for example, psoriasis of the genitalia; intergluteal, scrotal and inverse psoriasis; eczematized psoriasis of such areas as the ears, hands or feet, or cases in which other antipsoriatic remedies are not tolerated or not beneficial.

5. Seborrheic dermatitis; here the indications are similar to those in psoriasis, i. e ., when conditions such as superficial irritation and eczematization or maceration are present, in intertriginous sites, and when other conventional remedies irritate.

6. In pruritus ani, pruritus vulvae and other such pruritic conditions, when superficial infection, maceration and irritation play a role or when other remedies are ineffective or irritating.

7. Sycosis vulgaris, particularly when irritability, erythema or seborrheic features are an important part of the picture and eczematization, redness and greasy scaling are present in addition to the classic infected follicular lesions.

8. As a soothing and antiseptic application whenever a remedy is desired which is likely to be less irritating than other combinations of antiseptic and antiphlogistic agents.

The employment of "vioform" preparations in any of the aforementioned conditions does not preclude the concomitant use of other remedies. On the contrary, it is often desirable or necessary to employ such combined therapy as hot wet compresses or soaks with potassium permanganate several hours daily and "vioform" applications the remaining time or tinctures (such as Arning's tincture [anthrarobin, tumenol, ether and tincture of benzoin]) during the day and "vioform" applications at night.

In Europe the most commonly employed "vioform" preparation was an ointment consisting of 5 per cent "vioform" in petrolatum. This was applied and usually kept on under carefully fitted smooth linen or cotton bandages. One of us (M. B. S.) can recall no case of severe irritation and only a few of sensitization among the large series of patients in which this preparation was employed in Switzerland and Germany. On returning to the United States in 1929, one of us (M. B. S.) found that the 5 per cent concentration of "vioform" in petrolatum was apparently well tolerated here, also, until about the end of the year 1940. From that time on, occasional instances of irritation and sensitization were observed.

In an effort to establish the reasons for this change, it was learned that the manufacture of "vioform" in the United States had been started in May 1940 and that the process as used here yielded a finer lighter powder, with smaller particle sizes than the product formerly imported from Switzerland. On the assumption that this difference in physical properties would achieve a greater surface effect and would be more active per unit of weight, we lowered our routine concentration in petrolatum from 5 per cent to 3 per cent and, sometimes, even to 2 per cent or less. Thereafter the incidence of sensitizations again became negligible; "vioform" preparations having the lowered concentration are less sensitizing than most other antiseptics in common use (sulfonamide drugs, penicillin, mercurials, other quinoline derivatives). Nevertheless, rare cases of irritation or sensitization have occurred, and it is our impression that their incidence may be slightly higher here than in Europe.

While "vioform" in white petrolatum is to date by far our most commonly employed preparation, we have used "vioform" in shake lotions (e. g., zinc oxide, talc, glycerin, alcohol, water), in emulsions (e. g., calamine liniment N. F.), as a powder in talc and in other forms and vehicles.

"VIOFORM" IN WATER-WASHABLE CREAM

"Vioform" 3 per cent in white petrolatum makes a brownish, rather soft ointment which requires bandaging and which tends to produce yellowish staining of materials and of the surface of the skin. For these reasons, it seemed to us desirable to attempt to use "vioform" in a water-washable vanishing cream type vehicle which would not be so greasy, would not require bandaging and which might reduce the staining

properties of "vioform." For several years we studied the effects of "vioform" in 3 per cent concentration in a number of different oil-in-water emulsion cream vehicles. Although several acceptable creams were obtained, these preparations appeared to be more irritating than the same concentration of "vioform" in petrolatum.

In June 1945, we started to use a new preparation of "vioform" 3 per cent in a water-washable cream.[4] The vehicle used in this cream consists of:

Sodium lauryl sulfonate
Stearyl alcohol
Spermaceti
Glycerin
Petrolatum, yellow
Distilled water

One of the principal differences between this water-washable cream and those previously tried by us is that this cream is especially milled after the "vioform" has been added to the vehicle. This specially prepared and milled cream has now been used by us in a relatively large series of cases. Table 1 enumerates those cases encountered in our practice which could be followed sufficiently carefully and over a long enough period of time to permit an evaluation of effects.

TABLE 1.—*Cases Studied*

Condition	No. of Cases
Eczematous dermatitis, including secondarily infected cases (allergic and non-allergic eczematous dermatitis, dermatophytids, nummular eczemas, etc.)	55
Atopic dermatitis	24
Miscellaneous dermatoses (exfoliative erythroderma, pyoderma, intertrigo, etc.)	9
Psoriasis	8
Seborrheic dermatitis	6

Table 2 presents the results obtained in these 102 cases.

TABLE 2.—*Effect of "Vioform" 3 per Cent in Water-Washable Cream in 102 Cases*

Diagnosis	Total Number of Cases	Number of Cases with Good* Results	Number of Cases with Fair† Results	Number of Cases with Poor‡ Results	Number of Cases in Which Irritation Was Noted	Number of Cases in Which Sensitization Was Noted
Eczematous dermatitis	55	28	15	12	7	..
Atopic dermatitis	24	13	7	4	3	..
Miscellaneous dermatoses	9	..	5	4	2	..
Psoriasis	8	4	4	..	..	..
Seborrheic dermatitis	6	4	..	2	..	..

* Good results: The cream had a major share in bringing about healing of the eruption.
† Fair results: The cream brought improvement but was combined with or followed with other remedies in order to bring about final healing.
‡ Poor results: The cream did not bring about any improvement, the dermatosis remaining unchanged or getting worse.

4. The Ciba Pharmaceutical Co., Summit, N. J., supplied us with the Vioform cream used in this study.

SIDE EFFECTS OF "VIOFORM" PREPARATIONS

Primary Irritancy and Sensitization.—On "normal" skin "vioform" 3 per cent entirely lacks primary irritancy when applied in any of the various vehicles mentioned in the present report. As previously stated, the incidence of irritations and of sensitizations from the therapeutic use of "vioform" 3 per cent in petrolatum is low as compared with other commonly used dermatologic remedies. Table 2 shows that there were no cases of sensitization due to "vioform" among the 102 cases in the series treated with the 3 per cent preparation in the water-washable cream. We believe that these results indicate that the sensitizing index of this preparation is sufficiently low to compare favorably with that of "vioform" 3 per cent in petrolatum.

Incompatibilities.—"Vioform" can be combined with or used on areas previously treated with most of the commonly used topical agents, with the possible exception of mercury and sulfur. However, we do not recall observing any irritations after using the preparation on areas which twenty-four to forty-eight hours previously had been treated with mercury or sulfur. Still, it is theoretically possible that the small quantities of free iodine liberated by "vioform" might form irritating compounds with mercury and sulfur. Therefore, we believe that it is wise to let at least one day intervene between the successive use of "vioform" and mercury or sulfur on the same cutaneous area.

Systemic Toxicity.—The fact that "vioform" is safely administered by mouth and in the form of vaginal suppositories clearly indicates that under the usual conditions of dermatologic use there is no reason to fear toxic manifestations due to absorption. This point of view is supported by the lack of reports on systemic toxicity of the preparation after topical use and by the relatively low degree of toxicity observed in the pharmacologic studies of David, Phatak and Zener.[5] However, because of the possible rise of the iodine level in the blood after absorption of "vioform," the use of this drug over large areas may be contraindicated in some cases of iododermas and in dermatoses commonly associated with hypersensitivity to iodides, such as dermatitis herpetiformis, bromodermas or acne vulgaris.

COMMENT

In submitting these impressions of "vioform" in old and new vehicles we are fully aware that the correct and speedy evaluation of topical remedies for dermatologic therapy on the clinical material of a private practice or of a clinic is a difficult matter. A really scientific evaluation is often almost impossible, mainly because of the variability of response in

5. David, N. A.; Phatak, N. M., and Zener, F. B.: Iodochlorhydroxyquinoline and Di-Iodohydroxyquinoline: Animal Toxicity and Absorption in Man, Am. J. Trop. Med. **24**:29, 1944.

different cases or even different areas of the same dermatosis. For this reason it is usually impossible to compare the effects of a new remedy with those of an established "standard" treatment agent without employing almost astronomic numbers of cases in order to rule out chance variations. An evaluation of two treatment agents through their comparison on similarly affected symmetrically situated sites in the same persons has been employed by us for many years as perhaps the closest possible practical approach to a scientific study of topical treatment agents. Confirmatory work in this direction has been carried on independently by Siemens,[6] who refers to previous work on this method by Schweninger, Unna, Dreuw and Schäffer.

Although this fact could not be included in table 2, in many of our cases we have employed this method of paired comparison.[7] The results of such comparison of "vioform" preparations with other treatment agents and with the vehicle alone used on symmetrically situated similarly affected sites indicated that the drug is an effective and often superior treatment agent.

Despite the excellent impressions gained from our own evaluations and despite the decades of favorable clinical experience with "vioform" in white petrolatum, we by no means intend to imply that "vioform" is always an effective topical remedy, but only that it is another valuable agent to be included in the dermatologic armamentarium. In our experience the value of "vioform" in topical therapy ranges with that of such proved remedies as the tars, mercury, sulfur and resorcinol.

The choice of the vehicle in which "vioform" should be used in any particular case or area must be based on considerations similar to those governing the choice of the vehicle for other topically used agents. As previously stated, "vioform" 3 per cent in petrolatum is in general the most widely employed and useful "vioform" preparation, and the "vioform" in water-washable cream, while it has special indications, can by no means replace the more greasy preparation which is indicated in the many cases in which softening and occlusive effects and protective bandaging are desired. However, in the present report we wish to call attention to one mode of use which was found to be effective and particularly practical in a fairly large number of cases. In these cases, "vioform" 3 per cent in the water-washable cream was used during the day and "vioform" 3 per cent in petrolatum at night. This combination permits treatment during the day with "vioform" in a nonocclusive and relatively nonmessy form, which does not necessitate bandaging, and during the

6. Siemens, H. W.: Die Leistungsfähigkeit der Einseitenbehandlung in der experimentellen dermatologischen Therapie, Arch. Dermat. u. Syph. **183**:223, 1942.

7. Sulzberger, M. B.; Baer, R. L.; Kanof, A., and Lowenberg, C.: Methods for the Rapid Evaluation of the Beneficial and Harmful Effects of Agents Applied to the Human Skin, J. Invest. Dermat. **7**:227, 1946.

night with "vioform" in a more lubricating and occlusive form, which can easily be carried out under bandages, white cotton gloves or socks, whichever the case may require.

SUMMARY AND CONCLUSIONS

Both long clinical experience and the present studies indicate that "vioform" (5-chloro-7-iodo-8-hydroxyquinoline) is a valuable remedy in topical therapy. It is effective as well as relatively nonirritating and nontoxic and has a low sensitizing index. The principal indications for the dermatologic use of "vioform" preparations are selected cases of eczematous dermatitis, atopic dermatitis, bacterial and mycotic dermatoses, psoriasis, seborrheic dermatitis, sycosis vulgaris and other infected and irritated lesions.

The preparation can be employed topically in various vehicles. In our experience a petrolatum base and a special water-washable cream have been the two most effective and practical vehicles. In 102 consecutive cases in which the effects of "vioform" 3 per cent in the special water-washable cream could be adequately evaluated, the clinical effects were considered good in 49, fair in 31 and poor in 32.

ADDENDUM

Since submitting this report we have confirmed our observations in hundreds of additional cases. The results have strengthened our conviction that "vioform" preparations, while not panaceas, are among the most valuable local therapeutic agents with very low irritancy and a low index or potential of sensitization.

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TREATMENT OF PITYRIASIS ROSEA WITH NONSPECIFIC SUBSTANCES

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THIS REPORT is based on the observation and treatment of 270 patients suffering from pityriasis rosea. Injections of fungus extracts, staphylococcus toxoid and a sterile solution of lactalbumin in colloidal form were the therapeutic agents used, with isotonic sodium chloride solution U.S.P. as the control. These studies were started in and carried on from 1943.

Pityriasis rosea was first described as a separate entity by Gibert [1] in 1860. Since then numerous attempts were made to discover the cause with its resultant specific therapy. A great variety of observations have been published as to causation. A brief summary of these various concepts follows.

Many authors have expressed a belief in the infectious origin of pityriasis rosea. Vidal [2] in 1882 was the first to describe the presence of an organism in the scales, which he named Microsporon dispar. Brocq,[3] his pupil, described the initial plaque as such and stated that it might be caused by an unknown infectious agent, transmitted by flea bites. In 1893 Kaposi [4] discovered mycelia; in 1912 DuBois [5] found "microspora" in the scales of pityriasis rosea. Later Gougerot [6] saw spores in them, as did Photinos,[7] Covisa,[8] Joyeux,

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology of the New York Post-Graduate Medical School and Hospital (Dr. Marion B. Sulzberger, Director).

1. Gibert, C. M.: Traité pratique des maladies de la peau et de la syphilis, ed. 3, Paris, H. Plon, 1860, vol. 1, p. 402.

2. Vidal, E.: Du pityriasis circiné et marginé: Description de son mycoderme; le microsporon anomoeon (microsporon dispar), Ann. de dermat. et syph. **3**:22 (Jan.) 1882.

3. Brocq, L.: Note sur la plaque primitive du pityriasis rosé de Gibert, Ann. de dermat. et syph. **8**:615 (Oct.) 1887.

4. Kaposi, M. K.: Lehrbuch der Hautkrankheiten, Vienna, 1893.

5. Du Bois: Parasite cryptogamique des dermatoses érythémato-squameuses du type pityriasis rosé de Gibert, Ann. de dermat. et syph. **3**:32 (Jan.) 1912.

6. Gougerot, H.: Traitement du pityriasis rosé de Gibert par l'éosine, Bull. Soc. franc. de dermat. et syph. **44**:1708 (July) 1937.

7. Photinos, P.: Beitrag zur Natur der Pityriasis rosea, Dermat. Ztschr. **68**:187 (Jan.) 1934; abstracted, Wise, F., and Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1934, p. 565.

(Footnotes continued on next page)

Burnier and Duche.[9] Oppenheim[10] discovered oidium-like organisms in the herald patch and stated that the secondary lesions were probably produced by emboli of these organisms in the fine capillaries of the skin. Highman and Rulison[11] stated that pityriasis rosea, in their belief, was caused by an external infectious agent, the portal of entry of which was the herald spot. Görl and Voigt[12] stated the belief that pityriasis rosea was caused by Staphylococcus pyogenous albus. Wile[13] was able to produce an eruption similar to pityriasis rosea by transmission. Simon[14] and Thomson and Cumings[15] stated that pityriasis rosea was caused by a filtrable virus. Benedek[16] attributed pityriasis rosea to a constant endoparasite, which produces the eruption by hematogenous spread.

Lassar,[17] J. Jadassohn,[18] Veiel,[19] Wise and Sulzberger[20] and Pick[21] stated that pityriasis rosea in many cases followed shortly after the wearing of new, stored or humid clothing. MacKee,[22] Kogoj and

8. Covisa, S.: Pityriasis rosea Gibert, Dermat. Wchnschr. **56**:115 (Jan. 25) 1913.

9. Joyeux, Burnier and Duché: Recherches sur la nature mycosique du pityriasis rosé, Bull. Soc. franç. de dermat. et syph. **37**:1128 (July 10) 1930.

10. Oppenheim, M.: Ueber Pityriasis rosea, Verhandl. Gesellsch. d. deutsch. Naturforsch. u. Ärzte **79** (pt. 2):409, 1907; abstracted; Arch. f. Dermat. u. Syph. **88**:355, 1907.

11. Highman, W. J., and Rulison, R. H.: Pityriasis Rosea: A Few Simple Facts, Arch. Dermat. & Syph. **7**:163 (Feb.) 1923.

12. Görl, L., and Voigt, L.: Zur Aetiologie der Pityriasis rosea, München. med. Wchnschr. **71**:599 (May 2) 1924.

13. Wile, U. J.: Experimental Transmission of Pityriasis Rosea: Preliminary Report, Arch. Dermat. & Syph. **16**:185 (Aug.) 1927.

14. Simon, C.: Quelques réflexions et souvenirs sur le pityriasis rosé de Gibert, Bull. méd., Paris **50**:702 (Oct. 24) 1936.

15. Thomson, M. S., and Cumings, J. N.: Investigations into the Causation of Pityriasis Rosea, Brit. J. Dermat. **43**:617 (Dec.) 1931.

16. Benedek, T.: Syphilis and the Biotropic Skin Exanthems of Known Bacterial Hematogen-Endogenous Origin; Seborrheic Dermatitis, Pompholyx, Pityriasis Rosea, Psoriasis Vulgaris, Urol. & Cutan. Rev. **46**:409 (July) 1942; Schizosaccharomycosis: II. Clinical (Mycide) Forms; Pityriasis Rosea of Gibert; Its Etiology and Pathogenesis, Arch. Dermat. & Syph. **26**:397 (Sept.) 1932.

17. Lassar, O.: Ueber die Natur der Pityriasis rosea, Deutsche med. Wchnschr. **18**:469 (May 26) 1892.

18. Jadassohn, J., in Darier, J.: Grundriss der Dermatologie, translated by K. G. Zwick, Berlin, Julius Springer, 1913, p. 66.

19. Veiel, F.: Zur Kenntnis der Pityriasis rosea, Dermat. Ztschr. **62**:91 (Sept.) 1931; abstracted, Wise, F., and Sulzberger, M. B.: Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1931, p. 153.

20. Wise, F., and Sulzberger, M. B.: Editorial comment on Veiel[19]; Editorial comment on Photinos.[7]

21. Pick, E., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 7, pt. 1, p. 401.

22. MacKee, G. M.: Personal communication to the author.

Farkas,[23] Moingeard,[24] Thibierge,[25] Fox,[26] Pollitzer,[27] Pusey,[28] Kyrle,[29] Chevallier [30] and Wile [13] stated that pityriasis rosea behaved like the infectious exanthemas and belonged to that group. Feulard,[31] Szabóky [32] and Jaquet [33] expressed the belief that pityriasis rosea was of gastrointestinal origin. Hyde,[34] Alderson,[35] Szabóky [32] and Jaquet [33] observed that some of the cases of pityriasis rosea had a psychogenic or neurogenic background. Owens,[36] Little,[37] Mestchersky,[38] Haspel,[39] Hazen,[40] Pernet,[41] Dore [42] and MacLeod [43] saw cases in which the disease was preceded by, or associated with, tonsillitis. Le Damany [44] classed pityriasis rosea with the tuberculids.

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23. Kogoj, F., and Farkas, K.: Clinical Contribution on Pityriasis Rosea, Urol. & Cutan. Rev. **36**:451 (July) 1932.

24. Moingeard, A.: Etude sur le pityriasis rosé de Gibert, Thesis, Paris, no. 325, 1889.

25. Thibierge, G.: Pityriasis rosé, in Besnier, E.; Brocq, L., and Jacquet, L.: La Pratique dermatologique, Paris, Masson & Cie, 1900, vol. 3, p. 873.

26. Fox, G. H.: A Broader View of Pityriasis Rosea, J. A. M. A. **59**:493 (Aug. 17) 1912.

27. Pollitzer, S., in discussion on Highman and Rulison.[11]

28. Pusey, W. A.: The Principles and Practice of Dermatology, ed. 4, New York, D. Appleton & Company, 1924, p. 410.

29. Kyrle, J.: Vorlesungen über Histobiologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer, 1925-1927, vol. 1, p. 178.

30. Chevallier, P.: Une maladie souvent confondue avec la roséole syphilitique, le pityriasis rosé de Gibert, Hôpital **12**:661, 1924.

31. Feulard, H.: Pityriasis rosé de Gibert, dilatation de l' estomac, Ann. de dermat. et syph. **10**:459 (May 25) 1889.

32. Szabóky, J.: Beiträge zur Ätiologie der Pityriasis rosea, Monatsh. f. prakt. Dermat. **42**:495 (May 15) 1906.

33. Jaquet, cited by Pick.[21]

34. Hyde, cited by Alderson.[35]

35. Alderson, H. E.: Pityriasis Rosea: Clinical Observations, J. Cutan. Dis. **32**:353 (May) 1914.

36. Owens, W. D.: Observations on Pityriasis Rosea, J. Cutan. Dis. **32**:347 (May) 1914.

37. Little, E. G. G.: Discussion on Pityriasis Rosea, Proc. Roy. Soc. Med. **7**:121 (March) 1914.

38. Mestchersky, G.: Contribution à l' étiologie du pityriasis rosé de Gibert, Bull. Soc. franç. de dermat. et syph. **33**:148 (Feb. 11) 1926.

39. Haspel, K. L.: Angaben zur Ätiologie der pityriasis rosea, Dermat. Wchnschr. **102**:357 (March 21) 1936.

40. Hazen, H. H.: Late Observations on the Etiology and Treatment of Pityriasis Rosea, South. M. J. **24**:937 (Nov.) 1931.

41. Pernet, G., in discussion on Little.[37]

42. Dore, S. E., in discussion on Little.[37]

43. MacLeod, J. M. H., in discussion on Little.[37]

44. Le Damany, P.: Le pityriasis rosé de Gibert est une tuberculide, Presse méd. **27**:121 (March 10) 1919.

This large variety of theories led to varied therapeutic experiments. Besides treatment of pityriasis rosea with diverse topical remedies and physical agents, numerous attempts were made to treat it by means of parenteral methods.

Leiner [45] gave his patients intramuscular injections of milk. Stillians and Benedek administered intradermal injections of Benedek's vaccine. Gurvich [46] used subcutaneous injections of a streptococcus vaccine. Fidanza, Carrillo and Schujman [47] reported the intravenous use of a streptococcus vaccine. Niles and Klumpp [48] treated their patients with convalescent serum. Ebert and Otsuka [49] used typhoid vaccine by intramuscular route.

EXPERIMENTAL STUDIES

My patients ranged from 2 to 66 years of age, the average being 35 years. One hundred and fifty-one were female; 119 were male.

One hundred and seventy-seven of the patients had one herald patch; 16 patients had multiple herald patches, and 77 patients had none which were recognizable as such. Ninety patients suffered from itching. The face was involved in 39 patients, the neck in 80 and the scalp in 18. One patient had lesions of the oral mucosa (the Wassermann and Kahn reactions being negative). Six patients had cervical adenitis. The duration of the eruption when first observed varied between one and twenty weeks, the average being ten days. Eighty-one patients stated that they had worn new, stored or humid clothing within a short period before onset of the eruption. Forty-two had had gastrointestinal disturbances before or during the appearance of the pityriasis rosea lesions. Thirty-two gave a history of nervous upsets preceding or accompanying the disease. Two patients had pityriasis rosea for the second time within three years. These patients were treated in four groups.

Group 1.—Because the picture of pityriasis rosea is one often seen in dermatoses caused by fungi, I assumed that pityriasis rosea might be of fungous origin and decided to treat patients suffering from it with fungous extracts.

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45. Leiner, C.: Zur Behandlung der Pityriasis rosea im Kindesalter mit Milchinjektionen, Wien. med. Wchnschr. **71**:1802 (Oct. 15) 1921.

46. Gurvich, E. I.: Sur la clinique, la pathogénie et le traitement du pityriasis rosé de Gibert: Pityriasis rosea Gibert, Ann. de dermat. et syph. **7**:488 (May) 1936.

47. Fidanza, E. P.; Carrillo, F., and Schujman, S.: El tratamiento de la pitiriasis rosada de Gibert por las vacunas estreptocóccicas: Sus resultados, Semana méd. **1**:1048 (April 2) 1936.

48. Niles, H. D., and Klumpp, M. M.: Pityriasis Rosea: Review of the Literature and Report of Two Hundred and Nineteen Cases, in Thirty-Eight of Which Convalescent Serum Was Used, Arch. Dermat. & Syph. **41**:265 (Feb.) 1940.

49. Ebert, M. H., and Otsuka, M.: Treatment of Pityriasis Rosea by the Injection of Typhoid Vaccine, J. A. M. A. **123**:1036 (Dec. 18) 1943.

A. Ninety patients were treated with a 1:500 dilution of trichophyton extract.[50] All patients were tested for their sensitivity with 0.05 cc. of this extract intradermally, isotonic sodium chloride solution U.S.P. being used as a control. Of the 90 patients, 95 per cent proved nonsensitive to this dilution. Treatment was started forty-eight hours later. Four to six intradermal injections of the same dilution were given three times a week in increasing doses (0.1, 0.15, 0.2, 0.25, 0.3 and 0.35 cc.) over a period of two weeks.

Itching, whenever present, stopped after the second or third injection. The eruption disappeared entirely or was only faintly visible after three to six injections. Four patients did not improve. The result of this experiment was published in 1945 in the form of a preliminary report.[51]

B. In this group 60 patients were treated with a 1:500 dilution of Lederle's oidiomycin (a broth culture product of "Candida albicans"). Again all patients were tested for their sensitivity with 0.05 cc. of this extract intradermally, isotonic sodium chloride solution U.S.P. being used as a control. In contrast to the previous group treated with trichophyton extract, 90 per cent of these patients gave a positive reaction to "oidiomycin." Treatment was started forty-eight hours later. One tenth of a cubic centimeter was given intradermally twice a week; the dose was not increased. The results were slightly superior to those obtained in the previous group, treated with the trichophyton extract. The lesions began to involute or disappeared completely after the second or third injection. Pruritus, when present, ceased after one to two injections. Results were the same whether the eruption had been of a few days or of several (two to twelve) weeks' duration. In no case were ill effects noted from treatment. Two patients did not respond.

Group 2.—Since the good results with both the "trichophyton" and "oidiomycin" extracts might have been due to a nonspecific factor, a group of 30 patients were treated with staphylococcus toxoid (digest modified).[50] All patients were tested for their sensitivity with 0.05 cc. of this extract. Ninety-five per cent of them reacted positively. Treatment was started forty-eight hours later. All the patients were given 0.1 cc. of staphylococcus toxoid (digest modified) intradermally twice a week. The results were similar to those obtained with "oidiomycin." Pruritus was no longer present after one or two injections, and the eruption cleared up within seven to ten days. One patient showed no improvement.

Group 3.—This group consisted of 30 patients who received injections of a sterile solution of lactalbumin in colloidal form ("aolan," Duke Laboratories, Inc.).

A. Fifteen patients were given 0.1 cc. of this substance intradermally at two day intervals. When tested for their sensitivity, only 2 of them reacted positively. Four to six injections produced no change in the course of pityriasis rosea.

B. Fifteen patients received the same agent by intramuscular route. Amounts of 5 to 10 cc. were given in increasing doses twice a week, three to four injections in all. Each injection was followed by a rise of temperature (101-104 F.) within twenty-four hours. Pruritus ceased after the third injection. The eruption itself disappeared or became only faintly visible within twelve to fifteen days. Two patients showed no improvement.

Group 4.—Finally, simultaneously with each of the aforementioned groups of patients, those treated with trichophyton extract, "oidiomycin," staphylococcus toxoid (digest modified) and a sterile solution of lactalbumin in colloidal form, respectively,

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50. A product of Lederle Laboratories, Inc.

51. Vass, I.: Treatment of Pityriasis Rosea with Trichophyton Extract: A Preliminary Report, Arch. Dermat. & Syph. **51**:203 (March) 1945.

15 patients with pityriasis rosea (60 in all) were given 0.1 cc. of isotonic sodium chloride solution U.S.P. intradermally for control. In these patients the disease took its usual course. It lasted from three to eighteen weeks. Pruritus, whenever present, remained unchanged.

All patients were advised to avoid soap and to stop wearing tight garments for the duration of treatment, as the lesions tended to persist at sites of friction and pressure. When pruritus was present, an antipruritic emulsion was prescribed for topical use.

The therapeutic ineffectiveness of injections of isotonic sodium chloride solution in the control group suggests that the basis of improvement was not psychologic.

All patients underwent a thorough examination for pathogenic fungi. None could be found in the lesions of pityriasis rosea, either on direct examination or by culture. Improvement was most rapid in those patients who showed a pronounced allergic response when tested for their sensitivity to the substances used.

Review of my material on 270 patients treated with "trichophyton extract" of "oidiomycin," staphylococcus toxoid (digest modified) and a sterile solution of lactalbumin in colloidal form, respectively, leads me to conclude that, on the whole, the results obtained by their use in the treatment of pityriasis rosea are not due to any specific action.

SUMMARY

Two hundred and seventy patients were treated for pityriasis rosea in four groups. Group 1 *A* received 0.1 cc. of a highly diluted trichophyton extract intradermally in increasing doses three times a week, four to six injections being given in all. Group 1 *B* was given 0.1 cc. of a highly diluted "oidiomycin" (a broth culture product of Candida albicans) intradermally in equal doses twice a week, three to four injections in all. Group 2 received 0.1 cc. staphylococcus toxoid (digest modified) intradermally in equal doses twice a week, three to four injections being given in all. Group 3 *A* received 0.1 cc. of a sterile solution of lactalbumin in colloidal form, injected intradermally in equal doses at two day intervals. Four to six injections were given in all. Group 3 *B* received a sterile solution of lactalbumin in colloidal form by intramuscular route. Amounts of 5 to 10 cc. were given twice a week, two to four injections in all. Sixty patients, acting as controls, simultaneously with the patients in the aforementioned groups received intradermal injections of isotonic sodium chloride solution, U.S.P., 0.1 cc. twice a week for a total of four to six injections.

In all but 8 patients treated with trichophyton extract, "oidiomycin" and staphylococcus toxoid (digest modified), respectively (group 1 and group 2), pruritus ceased after the second or third injections. The eruption itself disappeared or became only faintly visible within seven to ten days.

Patients treated with a sterile solution of lactalbumin in colloidal form by intramuscular route responded somewhat more slowly. Pruritus ceased after the third injection. The eruption itself disappeared or became only faintly visible within twelve to fifteen days. Two patients

did not respond. Lactalbumin solution by intradermal route had no effect on the source of pityriasis rosea.

In contrast to the considerably shortened course of pityriasis rosea when the aforementioned substances were used, in the control groups given intradermal injections with isotonic sodium chloride or lactalbumin solution the condition took three to twenty weeks to clear up. These observations would appear to exclude the psychologic element as an essential factor in the favorable therapeutic response.

All patients who were treated with these extracts underwent a thorough examination for fungi. No recognized pathogenic fungi could

Summary of Results of Treatment

	Number of Patients Treated	Material Injected, Dosage	Number of Injections Given	Period Within Which Pruritus Ceased and Eruption Cleared
Group 1A	90	Trichophyton extract (Lederle Laboratories, Inc.); 0.1 cc. of a 1:500 dilution, intradermally 3 times a week	4-6	7-10 days
Group 1B	60	"Oidiomycin" (Lederle Laboratories, Inc.); 0.1 cc. of a 1:500 dilution, intradermally twice a week	2-4	7-10 days
Group 2	30	Staphylococcus toxoid (digest modified) (Lederle Laboratories, Inc.); 0.1 cc. intradermally twice a week	2-4	7-10 days
Group 3A	15	Sterile solution of lactalbumin in colloidal form ("aolan," Duke Laboratories, Inc.); 0.1 cc. intradermally 3 times a week	4-6	3-20 weeks
Group 3B	15	Sterile solution of lactalbumin in colloidal form ("aolan," Duke Laboratories, Inc.); 5-10 cc. by intramuscular route twice a week	3-4	12-15 days
Group 4 (control)	60	Isotonic sodium chloride solution U.S.P., 0.1 cc. intradermally twice a week	4-6	3-20 weeks

be found either on direct examination or by culture in the lesions of pityriasis rosea.

CONCLUSIONS

Good results were obtained with intradermal injections of trichophyton extract and "oidiomycin," staphylococcus toxoid (digest modified) and intramuscular injections of a sterile solution of lactalbumin in colloidal form, respectively, in the treatment of pityriasis rosea. No such results were obtained by intradermal injections of isotonic sodium chloride or lactalbumin solutions. The theory is expressed that the results were probably due to a nonspecific effect of the active substances. The investigative study of 270 patients did not show any evidence in favor of the fungous origin of pityriasis rosea.

TRICHONODOSIS

Report of a Case

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A CASE of trichonodosis (knotted hair) was reported in 1947 by Pratt.[1] To the present time that is the only report on this condition in the American literature. He quoted McCarthy [2] as stating that there are two types of trichonodosis: (1) a rare variety, occurring as solitary knots associated with abnormal hair growth, and (2) a commoner variety, occurring as single or multiple knots, resulting from mechanical forces.

Pratt's case was an example of the first variety. The following report deals with the "mechanical" type of trichonodosis, of which no account exists in the American literature.

REPORT OF A CASE

M. S., a 46 year old white man, was seen at the New York Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on March 10, 1948. He complained of generalized itching and "parasites on the skin" of two years' duration. Past treatment elsewhere consisted of the application of various ointments and shaving of all hair (except on the scalp) on two occasions.

Examination revealed an excitable, intensely worried, intelligent man. On most of the body was a moderately dense covering of hair of rather fine structure, but curly. No cutaneous lesions were discovered. Pruritus was referred to in all cutaneous areas below the neck. Furthermore, the patient insisted that he could feel the "parasites" on his hair. He did, in fact, quickly locate a hair on the thigh which on close inspection revealed a barely visible body on the hair shaft. Microscopic examination disclosed a tight knot, as illustrated in the figure. There was no demonstrable disease either of the skin or of the hair.

Further examination of the patient disclosed dozens of knotted hairs on the trunk, thighs, buttocks, pubes and scrotum. The scalp hair showed no knotting. The patient stated that he had always had curly hair and was troubled frequently

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1. Pratt, A. G.: Trichonodosis: Report of a Case, Arch. Dermat. & Syph. **56**:267 (Aug.) 1947.

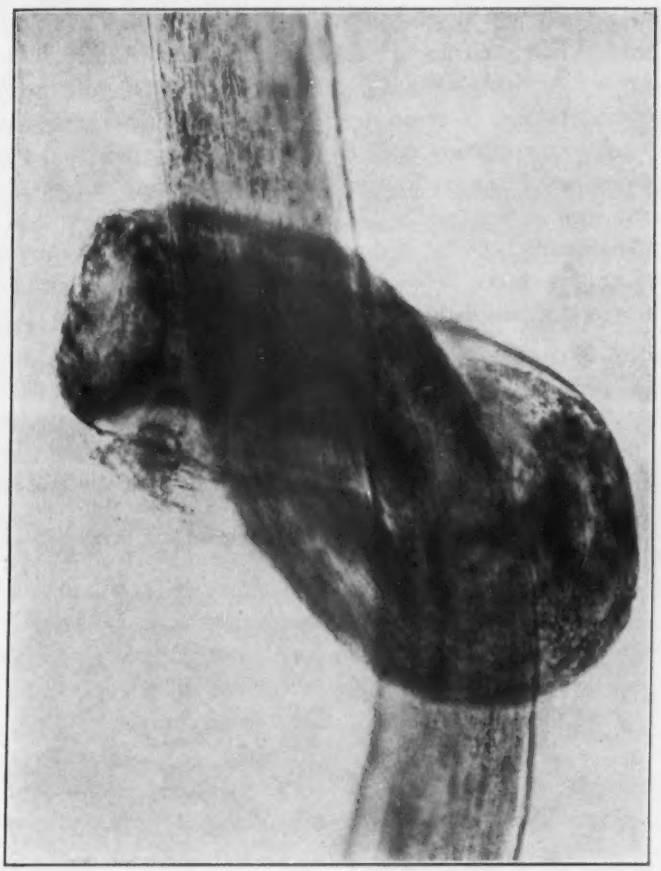
2. McCarthy, L.: Diagnosis and Treatment of Diseases of the Hair, St. Louis, C. V. Mosby Company, 1940, pp. 103-104.

by "ingrown hairs" in the bearded region. He admitted that his pruritus developed after he became aware of the nodes on his hairs. He had been convinced for two years that he was infested with some type of "bug."

The diagnosis was trichonodosis and delusion of parasitosis (acarophobia).

COMMENT

It is not intended to convey the idea that trichonodosis is a rare condition. On the contrary, it is extremely common. I have on many occasions



Photograph of a hair from the patient reported, showing typical knotting.

observed the presence of knotted hairs by chance while examining the skin closely. It seems to occur commonly in the pubic hairs. It causes no symptoms, and the patient is almost invariably unaware of its existence. After Galewsky [3] originally described the condition, Kren [4]

3. Galewsky: Ueber eine noch nicht beschriebene Haarekrankung (Trichonodosis), Arch. f. Dermat. u. Syph. **81**:195, 1906.

4. Kren, O.: Ueber das Vorkommen der Trichonodosis (Galewski), Wien. klin. Wchnschr. **20**:916, 1907.

found thirty-five instances of hair knotting in 54 women with various cutaneous diseases. In the only recent article on the subject (except that of Pratt [1]) Cajkovac [5] reported on 36 cases in which knotted hair was an incidental observation. He estimated that it occurs in about 10 per cent of patients with cutaneous diseases, particularly in pruriginous disease. He expressed the opinion that it was due to mechanical causes and was not dependent on skin changes or unequal hair growth.

I feel that, in cases of trichonodosis not associated with abnormal hair growth, curliness of the hair is an essential predisposing factor. Owing to the hair's curling, a loose knot is fortuitously formed. In patients, however, who scratch or rub the skin, who pull on the hairs or who constantly run their fingers through their hair, these loose knots are tightened to form a tiny node on the hair shaft; these nodes can then come into the patient's consciousness by virtue of their being felt or seen, as is exemplified in this case.

The paucity of reports dealing with this condition is undoubtedly due to its unimportance. However, it seems worthy of mention, if only to aid the recognition of the type of case herein described.

SUMMARY

A case of so-called mechanical type of trichonodosis (knotted hair) is reported. Its possible pathogenesis is briefly discussed. A severe degree of acarophobia was present in association with the hair knotting.

5. Cajkovac, S.: Morphology and Pathogenesis of Trichonodosis, Liječn. vjes. **61**:471, 1939.

PSORIASIS OF THE HYPOPHARYNX

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INVOLVEMENT of the mucous membrane in psoriasis is a most unusual feature of this disease. Though accepted by most leading authorities it has been seen only by a few. Usually it is the buccal mucosa (the cutaneous region of Jadassohn and Schuhmacher), the tongue, the palate and the lips that are involved.

Up to the time when Oppenheim first performed a biopsy in his case great confusion existed, since the terms leukoplakia and psoriasis buccalis (Bazin, 1868) were used synonymously. Since then, a goodly number of cases, with and without histologic examination, have been reported in publications or presented at dermatologic meetings.

Psoriasis of the conjunctiva and the vulva is even rarer than oral psoriasis, while involvement of the larynx is recorded in the literature only three times (Rugani, Paludetti). Rugani's patient had had psoriasis for many years. For the last three years that the condition existed, there was involvement of the larynx with each exacerbation of the cutaneous condition, as evidenced by pain and lowering of the voice. Laryngoscopic examination revealed small gray plaques on congested vocal cords. These lesions disappeared with the improvement of the cutaneous psoriasis. Rugani was able to see this phenomenon wax and wane five times in as many months. He quoted Paludetti as having seen 2 similar cases.

To our knowledge there is no case on record of psoriasis of the hypopharynx. Thus the following case was deemed worth reporting.

REPORT OF A CASE

A 60 year old man was admitted to The Mount Sinai Hospital because of progressive loss of vision. A craniotomy was performed, and a suprasellar meningioma was removed. The patient died three weeks later of massive pulmonary

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embolization. The following statements in his history are of importance. He had had psoriasis for forty-three years. He neither smoked nor drank. Reactions in repeated blood tests were negative for syphilis.

Apart from the aforementioned observations and some incidental observations, the autopsy showed a characteristic scaly pearly white psoriatic lesion on an erythematous base on the extensor surface of the left forearm. This area measured 12 cm. in its longest diameter. There was also a white fuzzy plaque 3 cm. in

Fig. 1.—Psoriatic plaque in right side of the hypopharynx.

diameter, surrounded by a red halo in the right pyriform recessus and on the adjacent wall of the hypopharynx (fig. 1).

No definite diagnosis could be made from the gross appearance of the lesion. The possibility of thrush had to be abandoned when smears and cultures failed to show Monilia organisms. Sections were taken from the cutaneous and mucosal lesions for histologic study. The former showed the characteristic appearance of an old psoriatic plaque, while the latter revealed a most unusual picture. Firstly, there was a large degree of accumulation and desquamation of nucleated squamous epithelial cells analogous to the parakeratosis of cutaneous psoriasis (fig. 2), accompanied with a focal disturbance of the stratified epithelium which in places

failed to show the normal prismatic basal cells. The prickle cell layer consisted of a few flattened cells in these areas.

Secondly, there was a conspicuous accumulation of amorphous eosinophilic material in the submucosa which appeared yellow in the Azan (Heidenhain) and van Gieson stains. This edematous infiltration contained collagen and elastin bundles that were widely spread apart (fig. 3). The normally scant papillae of this region were flattened out and obliterated by this edema. This accounted for the

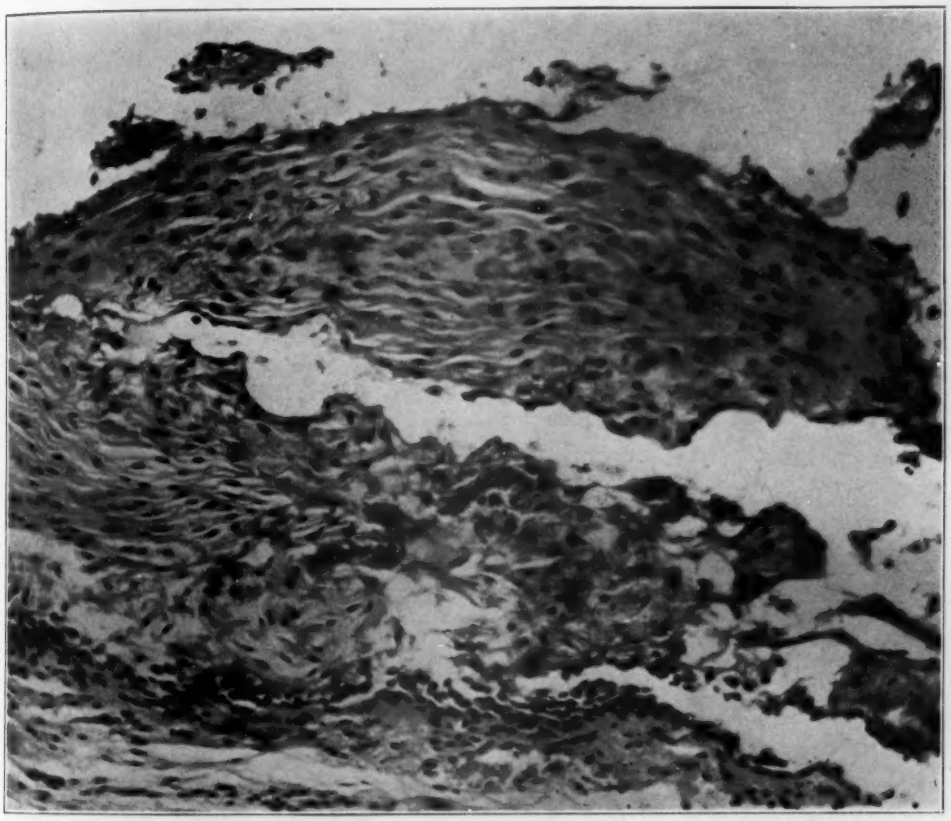

Fig. 2.—Pronounced piling up of nucleated squamous epithelium. The dark nuclei near the lower edge belong to epithelial cells (hematoxylin and eosin stain).

absence of acanthosis. The hyperemic ring of the lesion was explained by engorged submucosal vessels (fig. 4). (For a discussion of the halo of psoriatic lesions, see Herrmann and Kanof).

COMMENT

Some of the authors describing psoriasis of the mucous membrane have performed biopsies of these lesions. However, their microscopic observations were not uniform and, in some instances, were even contradictory. Most of the writers described parakeratosis. hypertrophy

of the epithelium (acanthosis), intercellular and intracellular edema, cellular infiltration and edema of the submucosa (corium) in varying degrees.

The unique localization of the lesion in our case accounts for the somewhat different histologic appearance. The submucosa of the hypopharynx and adjacent regions is unusually loose (as indicated by the

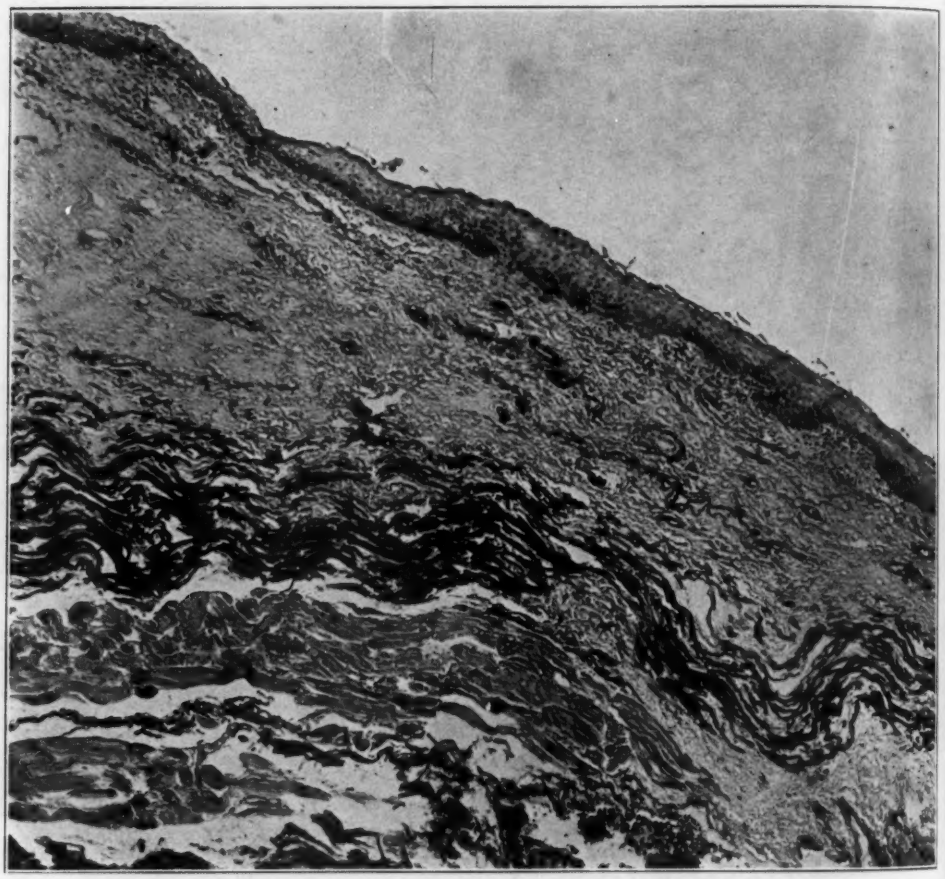

Fig. 3.—Edge of the lesion with almost normal epithelium. The submucosa is widened by edema which fades out to the right (Weigert-Van Gieson stain for elastin).

ease with which supraglottic edema develops in this site). The pathologist is familiar with the frequent agonal edema of these parts caused by the supine position of the body. It is this looseness of the submucosa which explains the exaggeration of the well known edema of psoriasis. This edema stretches the normally scant papillae of this region and flattens them out, and this makes quite comprehensible

the absence of the usual psoriatic acanthosis. The piling up of the epithelium and the large sheets of nucleated surface cells are analogous to what is seen in cutaneous psoriasis, as is the engorgement of the vessels. The fact that there was only a solitary psoriatic plaque on the skin does not militate against the diagnosis of psoriasis of the mucous membranes, since mucosal lesions may have a course independent of cutaneous exacerbations.

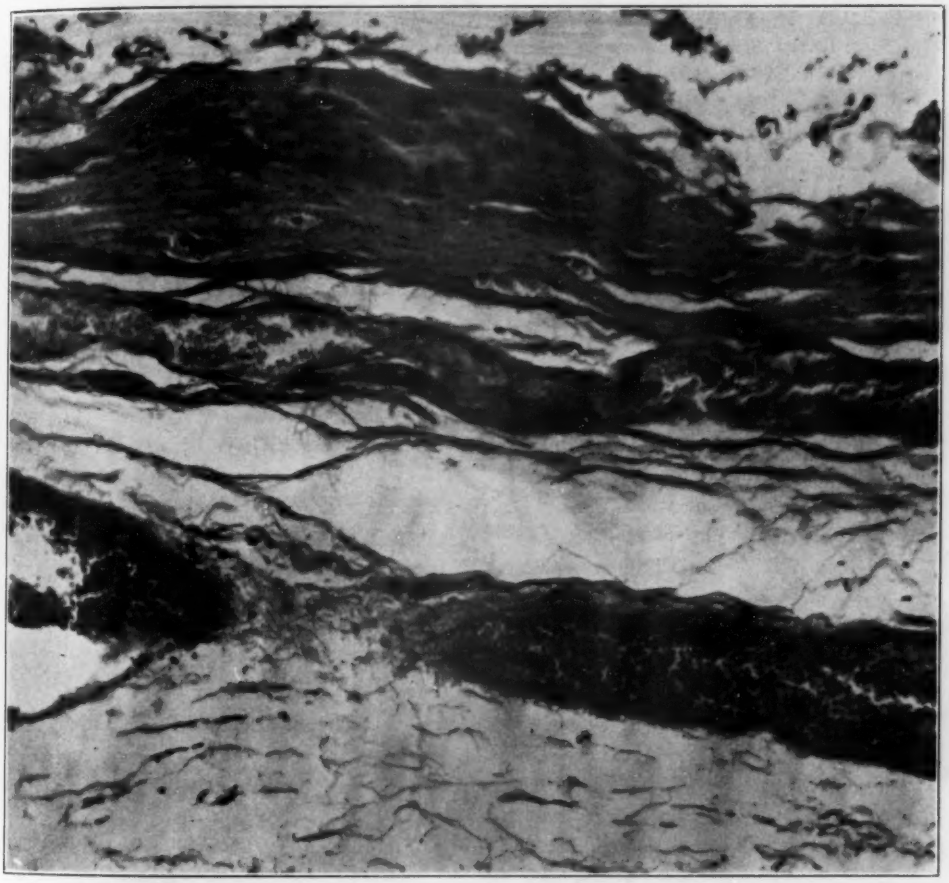

Fig. 4.—Engorged vessels arranged radially and parallel to the surface.

Leukoplakia is ruled out principally by the absence of a stratum granulosum and a stratum corneum.

SUMMARY

The first case of psoriasis of the hypopharynx is described and the differences in the microscopic picture accounted for by the looseness of the submucosa in this region. Hypertrophy of the epithelium

with parakeratosis and an impressive degree of edema of the submucosa dominate the histologic picture.

1 East One-Hundredth Street (29).
Atenas 3.

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Book Reviews

Occupational Marks and Other Physical Signs: A Guide to Personal Identification. By Francesco Ronchese, M.D. Price, $5.50. Pp. 181, with 151 illustrations. New York: Grune & Stratton, Inc., 1948.

This is an interesting book, which the author created as a result of his hobby of examining patients for evidence of occupational marks. He has surveyed workers in most of the industries and trades and in various professions and has recorded, with photographs and drawings, the marks on the skin acquired from their work. The possibility of using such marks for identification of the dead, as well as their value to criminal investigators, is stressed.

The illustrations are numerous and good. The book is recommended to physicians in general, but especially to dermatologists and to those whose knowledge of occupational marks should be essential in their work.